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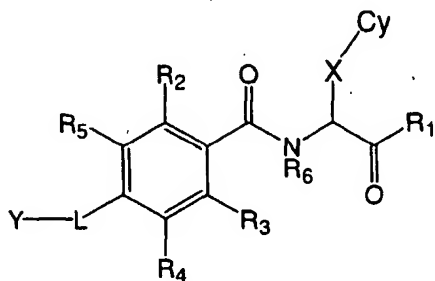
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South San Francisco, CA 94080 (US).(72) Inventors: **BURDICK, Daniel, J.**; 1404 Palm Drive,  
Burlingame, CA 94010 (US). **GADEK, Thomas, R.**; 2838  
Chelsea Drive, Oakland, CA 94611 (US). **MARSTERS**  
**James, C., Jr.**; 809 McKinley, Oakland, CA 94610 (US).  
**OARE, David**; 1622 Ralston Avenue, Belmont, CA 94002  
(US). **REYNOLDS, Mark, E.**; 175 Linda Vista, Millbrae,  
CA 94030 (US). **STANLEY, Mark, S.**; 284 Lauren  
Avenue, Pacifica, CA 94044 (US).(74) Agent: **EVANS, David, W.**; c/o Genentech, Inc., MS 49,  
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(54) Title: LFA-1 ANTAGONIST COMPOUNDS



(I)

(57) Abstract: The invention relates to novel compounds having formula (I), wherein Cy, X, Y, L and R1-6 are as defined herein. The compounds bind CD11/CD18 adhesion receptors such as Lymphocyte Function-associated Antigen-1 (LFA-1) and are therefore useful for treating disorders mediated by LFA-1 such as inflammation

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## LFA-1 ANTAGONIST COMPOUNDS

## FIELD OF THE INVENTION

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The invention relates to novel compounds which bind CD11/CD18 adhesion receptors, in particular Lymphocyte Function-associated Antigen-1 (LFA-1) as well as pharmaceutical compositions containing these compounds which are useful for treating disorders mediated thereby.

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## BACKGROUND OF THE INVENTION

25

## Inflammation

Human peripheral blood is composed principally of red blood cells, platelets and white blood cells or leukocytes. The family of leukocytes are further classified as neutrophils, lymphocytes (mostly B- and T-cell subtypes), monocytes, eosinophils and basophils. Neutrophils, eosinophils and basophils are sometimes referred to as "granulocytes" or "polymorphonuclear (PMN) granulocytes" because of the appearance of granules in their cytoplasm and their multiple nuclei. Granulocytes and monocytes are often classified as "phagocytes" because of their ability to phagocytose or ingest micro-organisms and foreign mater referred to generally as "antigens". Monocytes are so called because of their

30

35

5 large single nucleus and these cells may in turn become  
macrophages. Phagocytes are important in defending the  
host against a variety of infections and together with  
lymphocytes are also involved in inflammatory disorders.  
The neutrophil is the most common leukocyte found in  
10 human peripheral blood followed closely by the  
lymphocyte. In a microliter of normal human peripheral  
blood, there are about 6,000 leukocytes, of which about  
4,000 are neutrophils, 1500 are lymphocytes, 250 are  
monocytes, 150 are eosinophils and 25 are basophils.

15 During an inflammatory response peripheral blood  
leukocytes are recruited to the site of inflammation or  
injury by a series of specific cellular interactions (see  
Fig. 1). The initiation and maintenance of immune  
20 functions are regulated by intercellular adhesive  
interactions as well as signal transduction resulting  
from interactions between leukocytes and other cells.  
Leukocyte adhesion to vascular endothelium and migration  
from the circulation to sites of inflammation is a  
25 critical step in the inflammatory response (Fig. 1). T-  
cell lymphocyte immune recognition requires the  
interaction of the T-cell receptor with antigen (in  
combination with the major histocompatibility complex) as  
well as adhesion receptors, which promote attachment of  
30 T-cells to antigen-presenting cells and transduce signals  
for T-cell activation. The lymphocyte function  
associated antigen-1 (LFA-1) has been identified as the  
major integrin that mediates lymphocyte adhesion and  
activation leading to a normal immune response, as well  
35 as several pathological states (Springer, T.A., Nature  
346:425-434 (1990)). Intercellular adhesion molecules  
(ICAM) -1, -2, and -3, members of the immunoglobulin  
superfamily, are ligands for LFA-1 found on endothelium,

5 leukocytes and other cell types. The binding of LFA-1 to  
ICAMs mediate a range of lymphocyte functions including  
lymphokine production of helper T-cells in response to  
antigen presenting cells, T-lymphocyte mediated target  
10 cells lysis, natural killing of tumor cells, and  
immunoglobulin production through T-cell-B-cell  
interactions. Thus, many facets of lymphocyte function  
involve the interaction of the LFA-1 integrin and its  
ICAM ligands. These LFA-1:ICAM mediated interactions  
15 have been directly implicated in numerous inflammatory  
disease states including; graft rejection, dermatitis,  
psoriasis, asthma and rheumatoid arthritis.

While LFA-1 (CD11a/CD18) on lymphocytes plays a key role  
in chronic inflammation and immune responses, other  
20 members of the leukocyte integrin family (CD11b/CD18,  
CD11c/CD18 and CD11d/CD18) also play important roles on  
other leukocytes, such as granulocytes and monocytes,  
particularly in early response to infective agents and in  
acute inflammatory response.

25 The primary function of polymorphonuclear leukocytes,  
derived from the neutrophil, eosinophil and basophil  
lineage, is to sense inflammatory stimuli and to  
emigrate across the endothelial barrier and carry out  
30 scavenger function as a first line of host defense. The  
integrin Mac-1(CD11b/CD18) is rapidly upregulated on  
these cells upon activation and binding to its multiple  
ligands which results in the release of oxygen derived  
free radicals, protease's and phospholipases. In certain  
35 chronic inflammatory states this recruitment is  
improperly regulated resulting in significant cellular  
and tissue injury. (Harlan, J. M., *Acta Med Scand*



5      *Suppl.*, 715:123 (1987); Weiss, S., *New England J. of Med.*, 320:365 (1989)).

LFA-1 ( CD11a/CD18) and Mac-1 (CD11b/CD18)

10      The (CD11/CD18) family of adhesion receptor molecules comprises four highly related cell surface glycoproteins; LFA-1 (CD11a/CD18), Mac-1 (CD11b/CD18), p150.95 (CD11c/CD18) and (CD11d/CD18). LFA-1 is present on the surface of all mature leukocytes except a subset of macrophages and is considered the major lymphoid  
15      integrin. The expression of Mac-1, p150.95 and CD11d/CD18 is predominantly confined to cells of the myeloid lineage (which include neutrophils, monocytes, macrophage and mast cells). Functional studies have suggested that LFA-1 interacts with several ligands,  
20      including ICAM-1 (Rothlein et al., *J. Immunol.* 137:1270-1274 (1986), ICAM-2, (Staunton et al., *Nature* 339:361-364 (1989)), ICAM-3 (Fawcett et al., *Nature* 360:481-484 (1992); Vezeux et al., *Nature* 360:485-488, (1992); de Fougerolles and Springer, *J. Exp. Med.* 175:185-190  
25      (1990)) and Telencephalin (Tian et al., *J. Immunol.* 158:928-936 (1997)).

The CD11/CD18 family is related structurally and genetically to the larger integrin family of receptors  
30      that modulate cell adhesive interactions, which include; embryogenesis, adhesion to extracellular substrates, and cell differentiation (Hynes, R. O., *Cell* 48:549-554 (1987); Kishimoto et al., *Adv. Immunol.* 46:149-182 (1989); Kishimoto et al., *Cell* 48:681-690 (1987); Ruoslahti et al.,  
35      *Science* 238:491-497 (1987)).

Integrins are a class of membrane-spanning heterodimers comprising an  $\alpha$  subunit in noncovalent association with a

5         $\beta$  subunit.    The  $\beta$  subunits are generally capable of  
association with more than one  $\alpha$  subunit and the  
heterodimers sharing a common  $\beta$  subunit have been  
classified as subfamilies within the integrin population  
(Larson and Springer, "Structure and function of  
10        leukocyte integrins," *Immunol. Rev.* 114:181-217 (1990)).

The integrin molecules of the CD11/CD18 family, and their  
cellular ligands, have been found to mediate a variety of  
cell-cell interactions, especially in inflammation.  
15        These proteins have been demonstrated to be critical for  
adhesive functions in the immune system (Kishimoto et al.,  
*Adv. Immunol.* 46:149-182 (1989)). Monoclonal antibodies  
to LFA-1 have been shown to block leukocyte adhesion to  
endothelial cells (Dustin et al., *J. Cell. Biol.* 107:321-  
20        331 (1988); Smith et al., *J. Clin. Invest.* 83:2008-2017  
(1989)) and to inhibit T-cell activation (Kuypers et al.,  
*Res. Immunol.*, 140:461 (1989)), conjugate formation  
required for antigen-specific CTL killing (Kishimoto et  
al., *Adv. Immunol.* 46:149-182 (1989)), T. cell  
25        proliferation (Davignon et al., *J. Immunol.* 127:590-595  
(1981)) and NK cell killing (Krensky et al., *J. Immunol.*  
131:611-616 (1983)).

#### ICAMs

30        ICAM-1 (CD54) is a cell surface adhesion receptor that is  
a member of the immunoglobulin protein super-family  
(Rothlein et al., *J. Immunol.* 137:1270-1274 (1986);  
Staunton et al., *Cell* 52:925-933 (1988)). Members of this  
superfamily are characterized by the presence of one or  
35        more Ig homology regions, each consisting of a disulfide-  
bridged loop that has a number of anti-parallel  $\beta$ -pleated  
strands arranged in two sheets. Three types of homology

5 regions have been identified, each with a typical length  
and having a consensus sequence of amino acid residues  
located between the cysteines of the disulfide bond  
(Williams, A. F. et al. *Ann Rev. Immunol.* 6:381-405  
(1988); Hunkapillar, T. et al. *Adv. Immunol.* 44:1-63  
10 (1989). ICAM-1 is expressed on a variety of  
hematopoietic and non-hematopoietic cells and is  
upregulated at sites of inflammation by a variety of  
inflammatory mediators (Dustin et al., *J. Immunol.*,  
137:256-254 (1986)). ICAM-1 is a 90,000-110,000  $M_r$   
15 glycoprotein with a low messenger RNA levels and moderate  
surface expression on unstimulated endothelial cells.  
LPS, IL-1 and TNF strongly upregulate ICAM-1 mRNA and  
surface expression with peak expression at approximately  
18-24 hours (Dustin et al., *J. Cell. Biol.* 107:321-331  
20 (1988); Staunton et al., *Cell* 52:925-933 (1988)). ICAM-1  
has five extracellular Ig like domains (designated  
Domains 1, 2, 3, 4 and 5 or D1, D2, D3, D4 and D5) and an  
intracellular or cytoplasmic domain. The structures and  
sequence of the domains is described by Staunton et al.  
25 (Cell 52:925-933 (1988)).

ICAM-1 was defined originally as a counter-receptor for  
LFA-1 (Springer et al., *Ann. Rev. Immunol.* 5:223-252  
(1987); Marlin *Cell* 51:813-819 (1987); Simmons et al.,  
30 *Nature* 331:624-627 (1988); Staunton *Nature* 339:61-64  
(1989); Staunton et al., *Cell* 52:925-933 (1988)). The  
LFA-1/ICAM-1 interaction is known to be at least  
partially responsible for lymphocyte adhesion (Dustin  
et al., *J. Cell. Biol.* 107:321-331 (1988); Mentzer et al., *J.*  
35 *Cell. Physiol.* 126:285-290 (1986)), monocyte adhesion  
(Amaout et al., *J. Cell Physiol.* 137:305 (1988); Mentzer  
et al., *J. Cell. Physiol.* 130:410-415 (1987); te Velde et  
al., *Immunology* 61:261-267 (1987)), and neutrophil

5 adhesion (Loet *al.*, *J. Immunol.* 143(10):3325-3329 (1989);  
Smith *et al.*, *J. Clin. Invest.* 83:2008-2017 (1989)) to  
endothelial cells. Through the development of function  
blocking monoclonal antibodies to ICAM-1 additional  
ligands for LFA-1 were identified, ICAM-2 and ICAM-3  
10 (Simmons, *Cancer Surveys* 24, Cell Adhesion and Cancer,  
1995) that mediate the adhesion of lymphocytes to other  
leukocytes as well as non-hematopoietic cells.  
Interactions of LFA-1 with ICAM-2 are thought to mediate  
natural killer cell activity (Helander *et al.*, *Nature*  
15 382:265-267 (1996)) and ICAM-3 binding is thought to play  
a role in lymphocyte activation and the initiation of the  
immune response (Simmons, *ibid*). The precise role of  
these ligands in normal and aberrant immune responses  
remains to be defined.

20

#### Disorders Mediated by T Lymphocytes

Function blocking monoclonal antibodies have shown that  
LFA-1 is important in T-lymphocyte-mediated killing, T-  
helper lymphocyte responses, natural killing, and  
25 antibody-dependent killing (Springer *et al.*, *Ann. Rev.*  
*Immunol* 5:223-252 (1987)). Adhesion to the target cell  
as well as activation and signaling are steps that are  
blocked by antibodies against LFA-1.

30 Many disorders and diseases are mediated through T  
lymphocytes and treatment of these diseases have been  
addressed through many routes. Rheumatoid arthritis  
(RA) is one such disorder. Current therapy for RA  
includes bed rest, application of heat, and drugs.  
35 Salicylate is the currently preferred treatment drug,  
particularly as other alternatives such as  
immunosuppressive agents and adrenocorticosteroids can  
cause greater morbidity than the underlying disease

5       itself.   Nonsteroidal   anti-inflammatory   drugs   are  
available, and many of them have effective analgesic,  
anti-pyretic and anti-inflammatory activity in RA  
patients.   These include cyclosporin, indomethacin,  
10   phenylbutazone, phenylacetic acid derivatives such as  
ibuprofen and fenoprofen, naphthalene acetic acids  
(naproxen), pyrrolealkanoic acid (tometin), indoleacetic  
acids (sulindac), halogenated anthranilic acid  
(meclofenamate sodium), piroxicam, and diflunisal.  
15   Other drugs for use in RA include anti-malarials such as  
chloroquine, gold salts and penicillamine.   These  
alternatives frequently produce severe side effects,  
including retinal lesions and kidney and bone marrow  
toxicity.   Immunosuppressive agents such as methotrexate  
20   have been used only in the treatment of severe and  
unremitting RA because of their toxicity.  
Corticosteroids also are responsible for undesirable  
side effects (e.g., cataracts, osteoporosis, and  
Cushing's disease syndrome) and are not well tolerated  
in many RA patients.

25       Another disorder mediated by T lymphocytes is host  
rejection of grafts after transplantation.   Attempts to  
prolong the survival of transplanted allografts and  
xenografts, or to prevent host versus graft rejection,  
30   both in experimental models and in medical practice,  
have centered mainly on the suppression of the immune  
apparatus of the host/recipient.   This treatment has as  
its aim preventive immunosuppression and/or treatment of  
graft rejection.   Examples of agents used for preventive  
35   immunosuppression include cytotoxic drugs, anti-  
metabolites, corticosteroids, and anti-lymphocytic  
serum.   Nonspecific immunosuppressive agents found  
particularly effective in preventive immunosuppression

5 (azathioprine, bromocryptine, methylprednisolone,  
prednisone, and most recently, cyclosporin A) have  
significantly improved the clinical success of  
transplantation. The nephrotoxicity of cyclosporin A  
after renal transplantation has been reduced by co-  
10 administration of steroids such as prednisolone, or  
prednisolone in conjunction with azathioprine. In  
addition, kidneys have been grafted successfully using  
anti-lymphocyte globulin followed by cyclosporin A.  
Another protocol being evaluated is total lymphoid  
15 irradiation of the recipient prior to transplantation  
followed by minimal immunosuppression after  
transplantation.

Treatment of rejection has involved use of steroids, 2-  
20 amino-6-aryl-5-substituted pyrimidines, heterologous  
anti-lymphocyte globulin, and monoclonal antibodies to  
various leukocyte populations, including OKT-3. See  
generally *J. Pediatrics*, 111: 1004-1007 (1987), and  
specifically U.S. Pat. No. 4,665,077.

25 The principal complication of immunosuppressive drugs is  
infections. Additionally, systemic immunosuppression is  
accompanied by undesirable toxic effects (e.g.,  
nephrotoxicity when cyclosporin A is used after renal  
transplantation) and reduction in the level of the  
30 hemopoietic stem cells. Immunosuppressive drugs may  
also lead to obesity, poor wound healing, steroid  
hyperglycemia, steroid psychosis, leukopenia,  
gastrointestinal bleeding, lymphoma, and hypertension.

35 In view of these complications, transplantation  
immunologists have sought methods for suppressing immune  
responsiveness in an antigen-specific manner (so that

5        only the response to the donor alloantigen would be  
lost).        In addition, physicians specializing in  
autoimmune disease strive for methods to suppress  
autoimmune responsiveness so that only the response to  
10        the self-antigen is lost.        Such specific  
immunosuppression generally has been achieved by  
modifying either the antigenicity of the tissue to be  
grafted or the specific cells capable of mediating  
rejection.        In certain instances, whether immunity or  
tolerance will be induced depends on the manner in which  
15        the antigen is presented to the immune system.

Pretreating the allograft tissues by growth in tissue  
culture before transplantation has been found in two  
murine model systems to lead to permanent acceptance  
20        across MHC barriers.        Lafferty et al., *Transplantation*,  
22:138-149 (1976); Bowen et al., *Lancet*, 2:585-586  
(1979)..        It has been hypothesized that such treatment  
results in the depletion of passenger lymphoid cells and  
thus the absence of a stimulator cell population  
25        necessary for tissue immunogenicity.        Lafferty et al.,  
*Annu. Rev. Immunol.*, 1:143 (1983).        See also Lafferty et  
al., *Science*, 188:259-261 (1975) (thyroid held in organ  
culture), and Gores et al., *J. Immunol.*, 137:1482-1485  
(1986) and Faustman et al., *Proc. Natl. Acad. Sci.*  
30        *U.S.A.*, 78: 5156-5159 (1981) (islet cells treated with  
murine anti-Ia antisera and complement before  
transplantation).        Also, thyroids taken from donor  
animals pretreated with lymphocytotoxic drugs and gamma  
radiation and cultured for ten days *in vitro* were not  
35        rejected by any normal allogeneic recipient (Gose and  
Bach, *J. Exp. Med.*, 149:1254-1259 (1979)).        All of these  
techniques involve depletion or removal of donor  
lymphocyte cells.

5

In some models such as vascular and kidney grafts, there exists a correlation between Class II matching and prolonged allograft survival, a correlation not present in skin grafts (Pescovitz et al., *J.Exp.Med.*, 160:1495-1508 (1984); Conti et al., *Transplant. Proc.*, 19: 652-654 (1987)). Therefore, donor-recipient HLA matching has been utilized. Additionally, blood transfusions prior to transplantation have been found to be effective (Opelz et al., *Transplant. Proc.*, 4: 253 (1973); Persijn et al., *Transplant. Proc.*, 23:396 (1979)). The combination of blood transfusion before transplantation, donor-recipient HLA matching, and immunosuppression therapy (cyclosporin A) after transplantation was found to improve significantly the rate of graft survival, and the effects were found to be additive (Opelz et al., *Transplant. Proc.*, 17:2179 (1985)).

The transplantation response may also be modified by antibodies directed at immune receptors for MHC antigens (Bluestone et al., *Immunol. Rev.* 90:5-27 (1986)). Further, graft survival can be prolonged in the presence of antigraft antibodies, which lead to a host reaction that in turn produces specific immunosuppression (Lancaster et al., *Nature*, 315: 336-337 (1985)). The immune response of the host to MHC antigens may be modified specifically by using bone marrow transplantation as a preparative procedure for organ grafting. Thus, anti-T-cell monoclonal antibodies are used to deplete mature T-cells from the donor marrow inoculum to allow bone marrow transplantation without incurring graft-versus-host disease (Mueller-Ruchholtz et al., *Transplant Proc.*, 8:537-541 (1976)). In addition, elements of the host's lymphoid cells that



5 remain for bone marrow transplantation solve the problem of immunoincompetence occurring when fully allogeneic transplants are used.

10 As shown in Fig. 1, lymphocyte adherence to endothelium is a key event in the process of inflammation. There are at least three known pathways of lymphocyte adherence to endothelium, depending on the activation state of the T-cell and the endothelial cell. T-cell immune recognition requires the contribution of the T-cell  
15 cell receptor as well as adhesion receptors, which promote attachment of - cells to antigen-presenting cells and transduce regulatory signals for T-cell activation. The lymphocyte function associated (LFA) antigen-1 (LFA-1, CD11a/CD18,  $\alpha_L\beta_2$ : where  $\alpha_L$  is CD11a and  $\beta_2$  is CD18) has been identified as the major  
20 integrin receptor on lymphocytes involved in these cell adherence interactions leading to several pathological states. ICAM-1, the endothelial cell immunoglobulin-like adhesion molecule, is a known ligand for LFA-1 and  
25 is implicated directly in graft rejection, psoriasis, and arthritis.

LFA-1 is required for a range of leukocyte functions, including lymphokine production of helper T-cells in  
30 response to antigen-presenting cells, killer T-cell-mediated target cell lysis, and immunoglobulin production through T-cell/B-cell interactions. Activation of antigen receptors on T-cells and B-cells allows LFA-1 to bind its ligand with higher affinity.

35

Monoclonal antibodies (MAbs) directed against LFA-1 led to the initial identification and investigation of the

5 function of LFA-1 (Davignon et al., *J. Immunol.*, 127:590  
(1981)). LFA-1 is present only on leukocytes (Krensky  
et al., *J. Immunol.*, 131:611 (1983)), and ICAM-1 is  
distributed on activated leukocytes, dermal fibroblasts,  
and endothelium (Dustin et al., *J. Immunol.* 137:245  
10 (1986)).

Previous studies have investigated the effects of anti-  
CD11a MAbs on many T-cell-dependent immune functions *in*  
*vitro* and a limited number of immune responses *in vivo*.  
15 *In vitro*, anti-CD11a MAbs inhibit T-cell activation  
(Kuypers et al., *Res. Immunol.*, 140:461 (1989)), T-cell-  
dependent B-cell proliferation and differentiation  
(Davignon et al., *supra*; Fischer et al., *J. Immunol.*,  
136:3198 (1986)), target cell lysis by cytotoxic T-  
20 lymphocytes (Krensky et al., *supra*), formation of immune  
conjugates (Sanders et al., *J. Immunol.*, 137:2395  
(1986); Mentzer et al., *J. Immunol.*, 135:9 (1985)), and  
the adhesion of T-cells to vascular endothelium (Lo et  
al., *J. Immunol.*, 143:3325 (1989)). Also, the antibody  
25 5C6 directed against CD11b/CD18 was found to prevent  
intra-islet infiltration by both macrophages and T cells  
and to inhibit development of insulin-dependent diabetes  
mellitus in mice (Hutchings et al., *Nature*, 348: 639  
(1990)).

30 The observation that LFA-1:ICAM-1 interaction is  
necessary to optimize T-cell function *in vitro*, and that  
anti-CD11a MAbs induce tolerance to protein antigens  
(Benjamin et al., *Eur. J. Immunol.*, 18:1079 (1988)) and  
35 prolongs tumor graft survival in mice (Heagy et al.,  
*Transplantation*, 37: 520-523 (1984)) was the basis for  
testing the MAbs to these molecules for prevention of  
graft rejection in humans.

5

Experiments have also been carried out in primates. For example, based on experiments in monkeys it has been suggested that a MAb directed against ICAM-1 can prevent or even reverse kidney graft rejection (Cosimi et al.,  
10 "Immunosuppression of Cynomolgus Recipients of Renal Allografts by R6.5, a Monoclonal Antibody to Intercellular Adhesion Molecule-1," in Springer et al. (eds.), *Leukocyte Adhesion Molecules* New York: Springer, (1988), p. 274; Cosimi et al., *J. Immunology*,  
15 144:4604-4612 (1990)). Furthermore, the in vivo administration of anti-CD11a MAb to cynomolgus monkeys prolonged skin allograft survival (Berlin et al., *Transplantation*, 53: 840-849 (1992)).

20 The first successful use of a rat anti-murine CD11a antibody (25-3; IgG1) in children with inherited disease to prevent the rejection of bone-marrow-mismatched haploidentical grafts was reported by Fischer et al., *Lancet*, 2: 1058 (1986). Minimal side effects were  
25 observed. See also Fischer et al., *Blood*, 77: 249 (1991); van Dijken et al., *Transplantation*, 49:882 (1990); and Perez et al., *Bone Marrow Transplantation*, 4:379 (1989). Furthermore, the antibody 25-3 was effective in controlling steroid-resistant acute graft-  
30 versus-host disease in humans (Stoppa et al., *Transplant. Int.*, 4:3-7 (1991)).

However, these results were not reproducible in leukemic adult grafting with this MAb (Maraninchi et al., *Bone Marrow Transplant*, 4:147-150 (1989)), or with an anti-  
35 CD18 MAb, directed against the invariant chain of LFA-1, in another pilot study (Baume et al., *Transplantation*, 47: 472 (1989)). Furthermore, a rat anti-murine CD11a

5 MAb, 25-3, was unable to control the course of acute rejection in human kidney transplantation (LeMauff et al., *Transplantation*, 52: 291 (1991)).

10 A review of the use of monoclonal antibodies in human transplantation is provided by Dantal and Souillou, *Current Opinion in Immunology*, 3:740-747 (1991). An earlier report showed that brief treatment with either anti-LFA-1 or anti-ICAM-1 MAbs minimally prolonged the survival of primarily vascularized heterotopic heart  
15 allografts in mice (Isobe et al., *Science*, 255:1125 (1992)). However, combined treatment with both MAbs was required to achieve long-term graft survival in this model.

20 Independently, it was shown that treatment with anti-LFA-1 MAb alone potently and effectively prolongs the survival of heterotopic (ear-pinnae) nonprimarily vascularized mouse heart grafts using a maximum dose of 4 mg/kg/day and treatment once a week after a daily dose  
25 (Nakakura et al., *J. Heart Lung Transplant.*, 11:223 (1992)). Nonprimarily vascularized heart allografts are more immunogenic and more resistant to prolongation of survival by MAbs than primarily vascularized heart allografts (Warren et al., *Transplant. Proc.*, 5:717  
30 (1973); Trager et al., *Transplantation*, 47:587 (1989)). The latter reference discusses treatment with L3T4 antibodies using a high initial dose and a lower subsequent dose.

35 Another study on treating a sclerosis-type disease in rodents using similar antibodies to those used by Nakakura et al., *supra*, is reported by Yednock et al., *Nature*, 356:63-66 (1992). Additional disclosures on the

5 use of anti-LFA-1 antibodies and ICAM-1, ICAM-2, and  
ICAM-3 and their antibodies to treat LFA-1-mediated  
disorders include WO 91/18011 published 11/28/91, WO  
91/16928 published 11/14/91, WO 91/16927 published  
11/14/91, Can. Pat. Appln. 2,008,368 published 6/13/91,  
10 WO 90/03400, WO 90/15076 published 12/13/90, WO 90/10652  
published 9/20/90, EP 387,668 published 9/19/90, WO  
90/08187 published 7/26/90, WO 90/13281, WO 90/13316, WO  
90/13281, WO 93/06864, WO 93/21953, WO 93/13210, WO  
94/11400, EP 379,904 published 8/1/90, EP 346,078  
15 published 12/13/89, U.S. Pat. No. 5,002,869, U.S. Pat.  
No. 5,071,964, U.S. Pat. No. 5,209,928, U.S. Pat. No.  
5,223,396, U.S. Pat. No. 5,235,049, U.S. Pat. No.  
5,284,931, U.S. Pat. No. 5,288,854, U.S. Pat. No.  
5,354,659, Australian Pat. Appln. 15518/88 published  
20 11/10/88, EP 289,949 published 11/9/88, and EP 303,692  
published 2/22/89, EP 365,837, EP 314,863, EP 319,815,  
EP 468, 257, EP 362,526, EP 362, 531, EP 438,310.

Other disclosures on the use of LFA-1 and ICAM peptide  
25 fragments and antagonists include; U.S. Pat. No.  
5,149,780, U.S. Pat. No. 5,288,854, U.S. Pat. No.  
5,340,800, U.S. Pat. No. 5,424,399, U.S. Pat. No.  
5,470,953, WO 90/03400, WO 90/13316, WO 90/10652, WO  
91/19511, WO 92/03473, WO 94/11400, WO 95/28170, JP  
30 4193895, EP 314,863, EP 362,526 and EP 362,531.

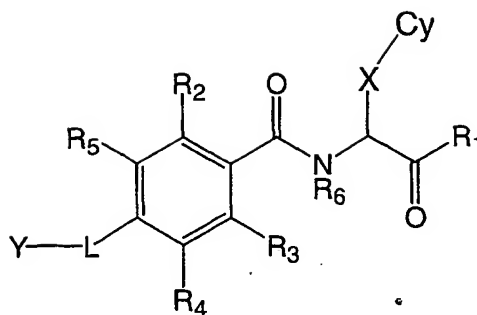
The above methods successfully utilizing anti-LFA-1 or  
anti-ICAM-1 antibodies, LFA-1 or ICAM-1 peptides,  
fragments or peptide antagonists represent an  
35 improvement over traditional immunosuppressive drug  
therapy. These studies demonstrate that LFA-1 and ICAM-  
1 are appropriate targets for antagonism. There is a  
need in the art to better treat disorders that are

5 mediated by LFA-1 including autoimmune diseases, graft  
vs. host or host vs. graft rejection, and T-cell  
inflammatory responses, so as to minimize side effects  
and sustain specific tolerance to self- or xenoantigens.  
There is also a need in the art to provide a non-peptide  
10 antagonists to the LFA-1: ICAM-1 interaction.

Albumin is an abundant plasma protein which is  
responsible for the transport of fatty acids. However,  
albumin also binds and perturbs the pharmacokinetics of a  
15 wide range of drug compounds. Accordingly, a significant  
factor in the pharmacological profile of any drug is its  
binding characteristics with respect to serum plasma  
proteins such as albumin. A drug compound may have such  
great affinity for plasma proteins that it is not be  
20 available in serum to interact with its target tissue,  
cell or protein. For example, a compound for which 99%  
binds to plasma protein upon administration will have  
half the concentration available in plasma to interact  
with its target than a compound which binds only 98%.  
25 Accordingly it would be desirable to provide LFA  
antagonist compounds which have low serum plasma protein  
binding affinity.

### 30 SUMMARY OF THE INVENTION

In an aspect of the present invention, there is provided  
novel compounds of formula (I)



(I)

wherein

Cy is a non-aromatic carbocycle or heterocycle optionally substituted with hydroxyl, mercapto, thioalkyl, halogen, oxo, thio, amino, aminoalkyl, amidine, guanidine, nitro, alkyl, alkoxy or acyl;

X is a divalent hydrocarbon chain optionally substituted with hydroxyl, mercapto, halogen, amino, aminoalkyl, nitro, oxo or thio and optionally interrupted with N, O, S, SO or SO<sub>2</sub>;

Y is a carbocycle or heterocycle optionally substituted with hydroxyl, mercapto, halogen, oxo, thio, a hydrocarbon, a halo-substituted hydrocarbon, amino, amidine, guanidine, cyano, nitro, alkoxy or acyl;

L is a bond or a divalent hydrocarbon optionally having one or more carbon atoms replaced with N, O, S, SO or SO<sub>2</sub> and optionally being substituted with hydroxyl, halogen oxo or thio; or three carbon atoms of the hydrocarbon are replaced with an amino acid residue;

R<sub>1</sub> is H, OH, amino, O-carbocycle or alkoxy optionally substituted with amino, a carbocycle or a heterocycle;

R<sub>2-5</sub> are independently H, hydroxyl, mercapto, halogen, cyano, amino, amidine, guanidine, nitro or alkoxy; or R<sub>3</sub> and R<sub>4</sub> together form a fused carbocycle or heterocycle optionally substituted with hydroxyl, halogen, oxo, thio, amino, amidine, guanidine or alkoxy;

- 5         $R_6$  is H or a hydrocarbon chain optionally substituted with a carbocycle or a heterocycle; and salts, solvates and hydrates thereof; with the proviso that when Y is phenyl,  $R_2$ ,  $R_4$  and  $R_5$  are H,  $R_3$  is Cl and  $R_1$  is OH then X is other than cyclohexyl.

10

In another aspect of the invention, there is provided pharmaceutical compositions comprising a compound of the invention and a pharmaceutically acceptable carrier.

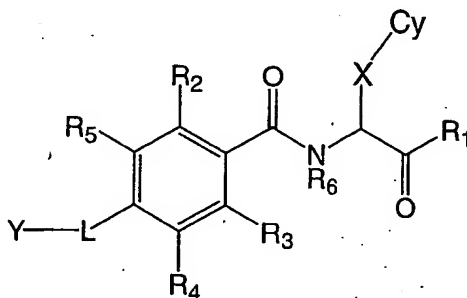
15

In another aspect of the invention, there is provided a method of treating a disease or condition mediated by LFA-1 in a mammal comprising administering to said mammal an effective amount of a compound of the invention.

20

#### DETAILED DESCRIPTION OF THE INVENTION

The invention provides novel compounds of formula (I)



25

(I)

- wherein Cy, X, Y, L and  $R_{1-6}$  are as defined herein. Compounds of the invention exhibit reduced plasma protein binding affinity by virtue of a non-aromatic ring at substituent Cy in comparison to those having an aromatic ring at this portion of the molecule.

30



5       The term "non-aromatic" refers to carbocycle or heterocycle rings that do not have the properties which define aromaticity. For aromaticity, a ring must be planar, have p-orbitals that are perpendicular to the plane of the ring at each ring atom and satisfy the  
10       Huckel rule where the number of pi electrons in the ring is  $(4n+2)$  wherein  $n$  is an integer (i.e. the number of pi electrons is 2, 6, 10 or 14). Non-aromatic rings provided herein do not satisfy one or all of these criteria for aromaticity.

15       The term "alkoxy" as used herein includes saturated, i.e. O-alkyl, and unsaturated, i.e. O-alkenyl and O-alkynyl, group. Exemplary alkoxy groups include methoxy, ethoxy, propoxy, butoxy, i-butoxy, s-butoxy, t-butoxy, pentyloxy  
20       and hexyloxy.

      The term "amino" refers to a primary ( $-NH_2$ ), secondary ( $-NHR$ ), tertiary ( $-N(R)_2$ ) or quaternary ( $-N^+(R)_4$ ) amine wherein  $R$  is a hydrocarbon chain, hydroxy, a carbocycle,  
25       a heterocycle or a hydrocarbon chain substituted with a carbocycle or heterocycle.

      The term "amino acid" refers to naturally and non-naturally occurring  $\alpha$ -(alpha),  $\beta$ -(beta), D- and L-amino  
30       acid residues. Non-natural amino acids include those having side chains other than those occurring in nature.

      By "carboxyl" is meant herein to be a free acid  $-COOH$  as well as esters thereof such as alkyl, aryl and aralkyl  
35       esters. Preferred esters are methyl, ethyl, propyl, butyl, i-butyl, s-butyl and t-butyl esters.

5     The term "carbocycle" refers to a mono-, bi- or tri-  
cyclic carbon ring or ring system having 4-16 members  
(including bridged) which is saturated, unsaturated or  
partially unsaturated including aromatic (aryl) ring  
systems (unless specified as non-aromatic). Preferred  
10   non-aromatic carbocyclic rings include cyclopropyl,  
cyclopropenyl, cyclobutyl, cyclobutenyl, cyclopentyl,  
cyclopentenyl, cyclohexyl and cyclohexenyl. Preferred  
aromatic carbocyclic rings include phenyl and naphthyl.

15   The term "heterocycle" refers to a mono-, bi- or tri-  
cyclic ring system having 5-16 members wherein at least  
one ring atom is a heteroatom (i.e. N, O and S as well as  
SO, or SO<sub>2</sub>). The ring system is saturated, unsaturated or  
partially unsaturated and may be aromatic (unless  
20   specified as non-aromatic). Exemplary heterocycles  
include piperidine, piperazine, pyridine, pyrazine,  
pyrimidine, pyridazine, morpholine, pyran, pyrrole, furan,  
thiophene (thienyl), imidazole, pyrazole, thiazole,  
isothiazole, dithiazole, oxazole, isoxazole, dioxazole,  
25   thiadiazole, oxadiazole, tetrazole, triazole,  
thiatriazole, oxatriazole, thiadiazole, oxadiazole,  
purine and benzofused derivatives thereof.

30   The term "hydrocarbon chain" refers to saturated,  
unsaturated, linear or branched carbon chains i.e. alkyl,  
alkenyl and alkynyl. Preferred hydrocarbon chains  
incorporate 1-12 carbon atoms, more preferably 1-6 and  
most preferably 1-4 carbon atoms i.e. methyl, ethyl,  
propyl, butyl and allyl.

35

The phrase "optionally substituted with" is understood to  
mean, unless otherwise stated, that one or more of the  
specified substituents is covalently attached to the

5 substituted moiety. When more than one, the substituents may be the same or different group.

Cy is a non-aromatic carbocycle or heterocycle optionally substituted with hydroxyl (-OH), mercapto (-SH),  
10 thioalkyl, halogen (e.g. F, Cl, Br, I), oxo (=O), thio (=S), amino, aminoalkyl, amidine (-C(NH)-NH<sub>2</sub>), guanidine (-NH<sub>2</sub>-C(NH)-NH<sub>2</sub>), nitro, alkyl or alkoxy. In a particular embodiment, Cy is a 3-5 member ring. In a preferred embodiment, Cy is a 5- or 6-member non-aromatic  
15 heterocycle optionally substituted with hydroxyl, mercapto, halogen (preferably F or Cl), oxo (=O), thio (=S), amino, amidine, guanidine, nitro, alkyl or alkoxy. In a more preferred embodiment, Cy is a 5-member non-aromatic heterocycle optionally substituted with  
20 hydroxyl, oxo, thio, Cl, C<sub>1-4</sub> alkyl (preferably methyl), or C<sub>1-4</sub> alkanoyl (preferably acetyl, propanoyl or butanoyl). More preferably the non-aromatic heterocycle comprises one or heteroatoms (N, O or S) and is optionally substituted with hydroxyl, oxo, mercapto,  
25 thio, methyl, acetyl, propanoyl or butyl. In particular embodiments the non-aromatic heterocycle comprises at least one nitrogen atom that is optionally substituted with methyl or acetyl. In a particularly preferred embodiment, the non-aromatic heterocycle is selected from  
30 the group consisting of piperidine, piperazine, morpholine, tetrahydrofuran, tetrahydrothiophene, oxazolidine, thiazolidine optionally substituted with hydroxy, oxo, mercapto, thio, alkyl or alkanoyl. In a most preferred embodiment Cy is a non-aromatic  
35 heterocycle selected from the group consisting of tetrahydrofuran-2-yl, thiazolidin-5-yl, thiazolidin-2-one-5-yl, and thiazolidin-2-thione-5-yl and cyclopropapyrrolidine.

5

In another preferred embodiment Cy is a 3-6 member carbocycle optionally substituted with hydroxyl, mercapto, halogen, oxo, thio, amino, amidine, guanidine, alkyl, alkoxy or acyl. In a particular embodiment the carbocycle is saturated or partially unsaturated. In particular embodiments Cy is a carbocycle selected from the group consisting of cyclopropyl, cyclopropenyl, cyclobutyl, cyclobutenyl, cyclopentyl, cyclopentenyl, cyclohexyl and cyclohexenyl.

15

X is a C<sub>1-5</sub> divalent hydrocarbon linker optionally having one or more carbon atoms replaced with N, O, S, SO or SO<sub>2</sub> and optionally being substituted with hydroxyl, mercapto, halogen, amino, aminoalkyl, nitro, oxo or thio. In a preferred embodiment X will have at least one carbon atom. Replacements and substitutions may form an amide moiety (-NRC(O)- or -C(O)NR-) within the hydrocarbon chain or at either or both ends. Other moieties include sulfonamide (-NRSO<sub>2</sub>- or -SO<sub>2</sub>NR), acyl, ether, thioether and amine. In a particularly preferred embodiment X is the group -CH<sub>2</sub>-NR<sub>6</sub>-C(O)- wherein the carbonyl -C(O)- portion thereof is adjacent (i.e. covalently bound) to Cy and R<sub>6</sub> is alkyl i.e. methyl and more preferably H.

30

Y is a carbocycle or heterocycle optionally substituted with hydroxyl, mercapto, halogen, oxo, thio, a hydrocarbon, a halo-substituted hydrocarbon, amino, amidine, guanidine, cyano, nitro, alkoxy or acyl. In particular embodiment, Y is aryl or heteroaryl optionally substituted with halogen or hydroxyl. In a particularly preferred embodiment, Y is phenyl, furan-2-yl, thiophene-

35

5 2-yl, phenyl substituted with a halogen (preferably Cl) or hydroxyl, preferably at the meta position.

L is a divalent hydrocarbon optionally having one or more carbon atoms replaced with N, O, S, SO or SO<sub>2</sub> and optionally being substituted with hydroxyl, halogen oxo, or thio; or three carbon atoms of the hydrocarbon are replaced with an amino acid residue. Preferably L is less than 10 atoms in length and more preferably 5 or less and most preferably 5 or 3 atoms in length. In particular embodiments, L is selected from the group consisting of -CH=CH-C(O)-NR<sub>6</sub>-CH<sub>2</sub>-, -CH<sub>2</sub>-NR<sub>6</sub>-C(O)-, -C(O)-NR<sub>6</sub>-CH<sub>2</sub>-, -CH(OH)-(CH<sub>2</sub>)<sub>2</sub>-, -(CH<sub>2</sub>)<sub>2</sub>-CH(OH)-, -(CH<sub>2</sub>)<sub>3</sub>-, -C(O)-NR<sub>6</sub>-CH(R<sub>7</sub>)-C(O)-NR<sub>6</sub>-, -NR<sub>6</sub>-C(O)-CH(R<sub>7</sub>)-NR<sub>6</sub>-C(O)-, -CH(OH)-CH<sub>2</sub>-O- and -CH(OH)-CF<sub>2</sub>-CH<sub>2</sub>- wherein each R<sub>6</sub> is independently H or alkyl and R<sub>7</sub> is an amino acid side chain. Preferred amino acid side chains include non-naturally occurring side chains such as phenyl or naturally occurring side chains. Preferred side chains are those from Phe, Tyr, Ala, Gln and Asn. In a preferred embodiments L is -CH=CH-C(O)-NR<sub>6</sub>-CH<sub>2</sub>- wherein the -CH=CH- moiety thereof is adjacent (i.e. covalently bound) to Y. In another preferred embodiment, L is -CH<sub>2</sub>-NR<sub>6</sub>-C(O)- wherein the methylene moiety (-CH<sub>2</sub>-) thereof is adjacent to Y.

30 R<sub>1</sub> is H, OH, amino, O-carbocycle or alkoxy optionally substituted with amino, a carbocycle or a heterocycle. In a preferred embodiment, R<sub>1</sub> is H, phenyl or C<sub>1-4</sub> alkoxy optionally substituted with a carbocycle such as phenyl. In a particular embodiment R<sub>1</sub> is H. In another particular embodiment R<sub>1</sub> is methoxy, ethoxy, propyloxy, butyloxy, isobutyloxy, s-butyloxy, t-butyloxy, phenoxy or benzyloxy. In yet another particular embodiment R<sub>1</sub> is

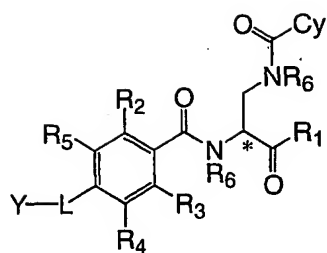
5     NH<sub>2</sub>. In a particularly preferred embodiment R<sub>1</sub> is ethoxy.  
In another particularly preferred embodiment R<sub>1</sub> is  
isobutyloxy. In another particularly preferred  
embodiment R<sub>1</sub> is alkoxy substituted with amino, for  
example 2-aminoethoxy, N-morpholinoethoxy, N,N-  
10     dialkylaminoethoxy, quaternary ammonium hydroxy alkoxy  
(e.g. trimethylammoniumhydroxyethoxy).

R<sub>2-5</sub> are independently H, hydroxyl, mercapto, halogen,  
cyano, amino, amidine, guanidine, nitro or alkoxy; or R<sub>3</sub>  
15     and R<sub>4</sub> together form a fused carbocycle or heterocycle  
optionally substituted with hydroxyl, halogen, oxo, thio,  
amino, amidine, guanidine or alkoxy. In a particular  
embodiment R<sub>2</sub> and R<sub>3</sub> are independently H, F, Cl, Br or I.  
In another particular embodiment, R<sub>4</sub> and R<sub>5</sub> are both H.  
20     In another particular embodiment, one of R<sub>2</sub> and R<sub>3</sub> is a  
halogen while the other is hydrogen or a halogen. In a  
particularly preferred embodiment, R<sub>3</sub> is Cl while R<sub>2</sub>, R<sub>4</sub>  
and R<sub>5</sub> are each H. In another particularly preferred  
embodiment, R<sub>2</sub> and R<sub>3</sub> are both Cl while R<sub>4</sub> and R<sub>5</sub> are both  
25     H.

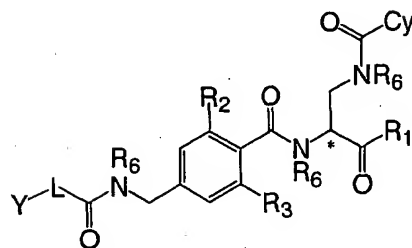
R<sub>6</sub> is H or a hydrocarbon chain optionally substituted with  
a carbocycle or a heterocycle. In a preferred  
embodiment, R<sub>6</sub> is H or alkyl i.e. methyl, ethyl, propyl,  
30     butyl, i-butyl, s-butyl or t-butyl. In a particular  
embodiment R<sub>6</sub> is H.

In a preferred embodiment, compounds of the invention  
have the general formula (Ia) - (If)

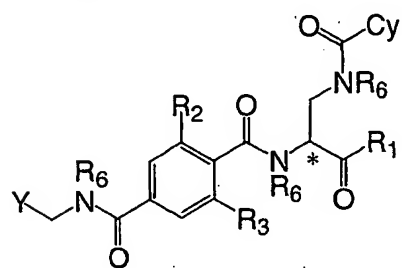
(Ia)



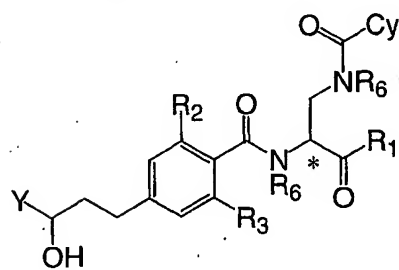
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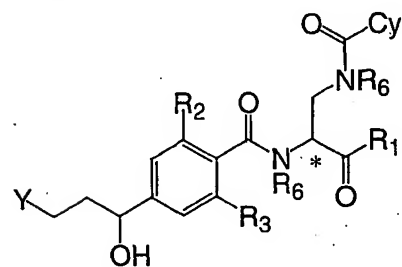
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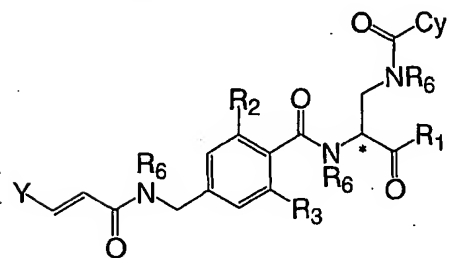
(Id)



(Ie)

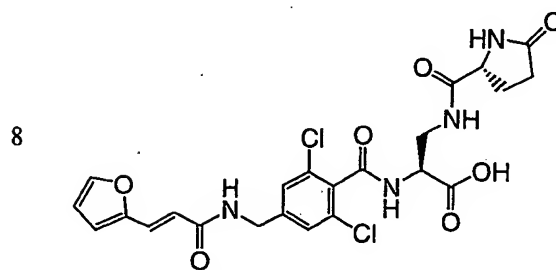
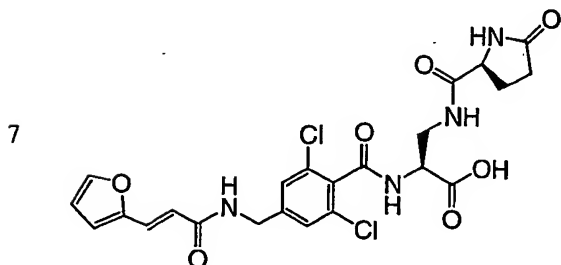
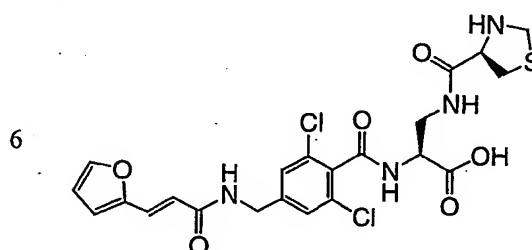
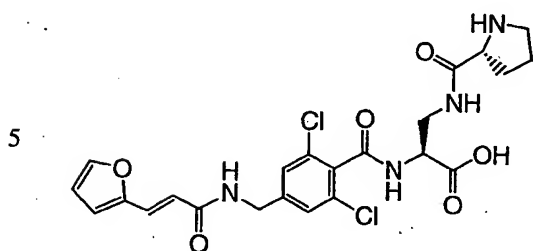
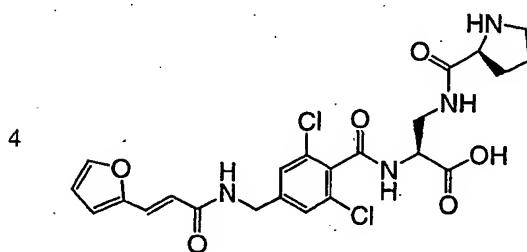
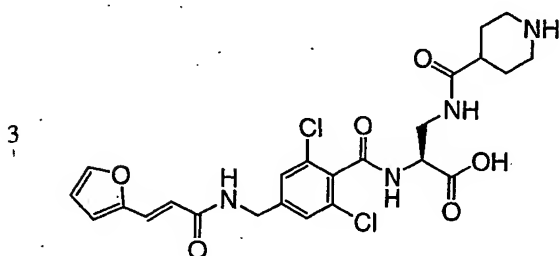
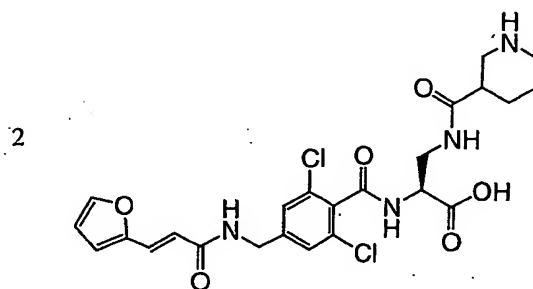
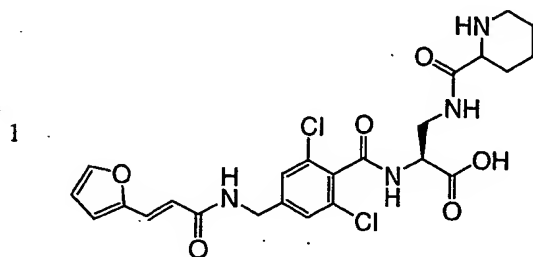


(If)

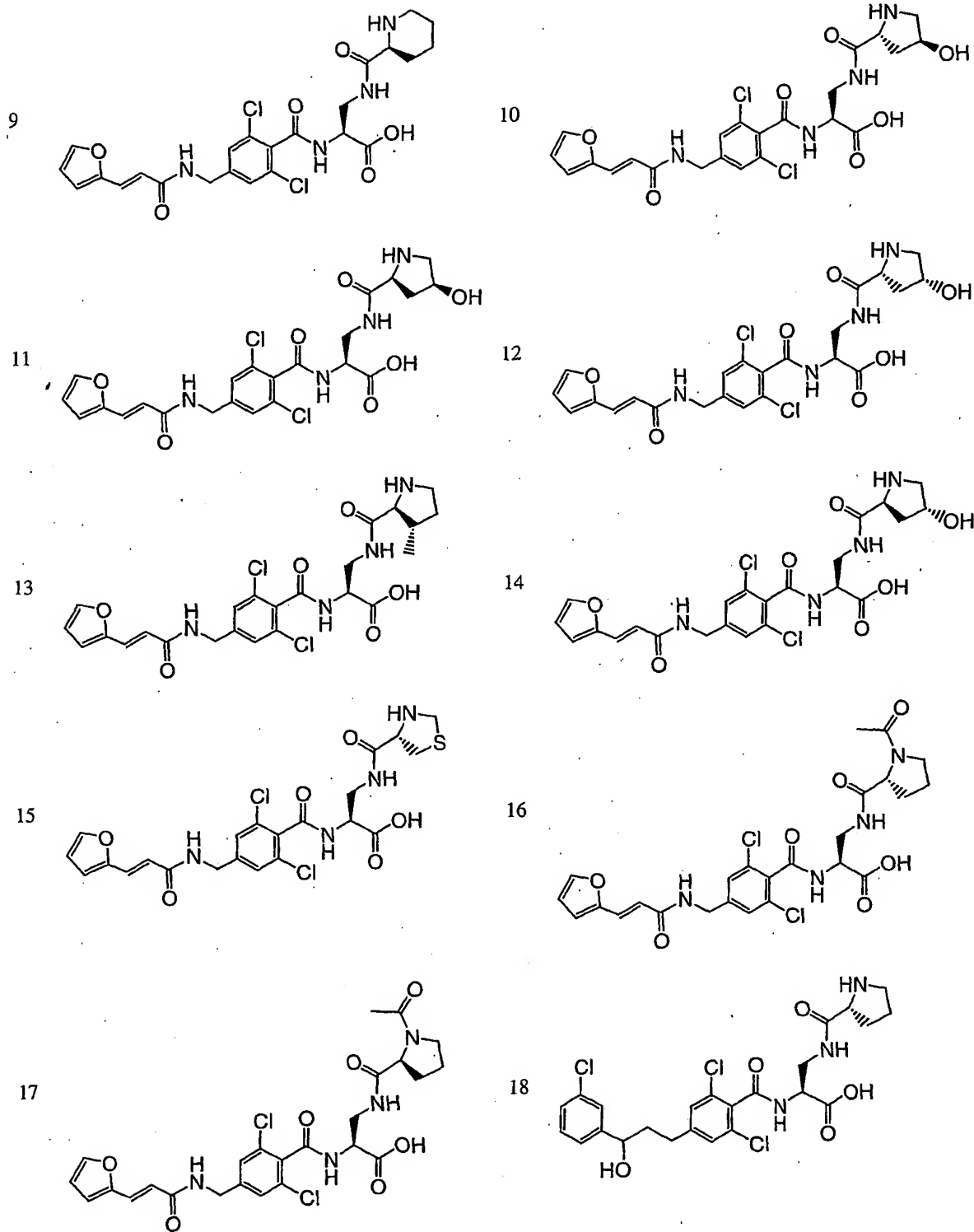


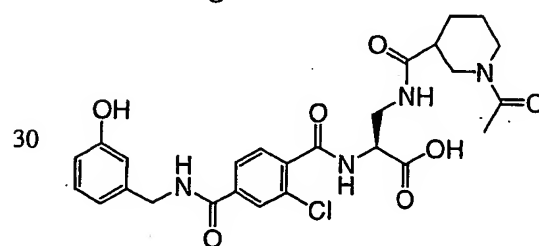
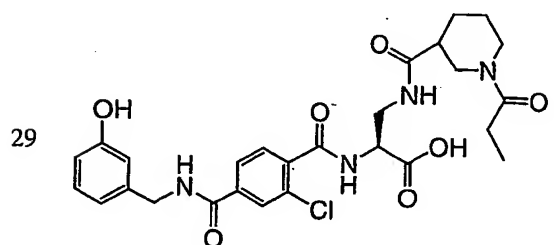
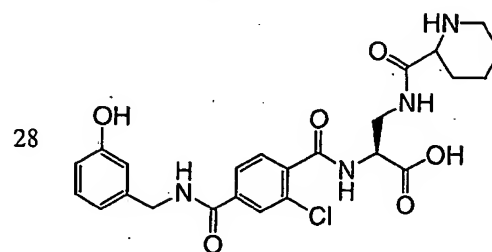
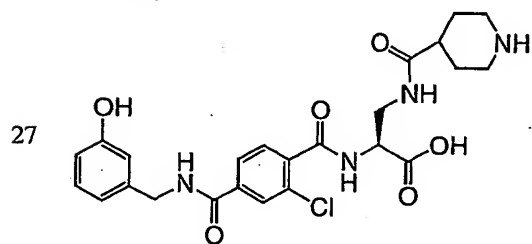
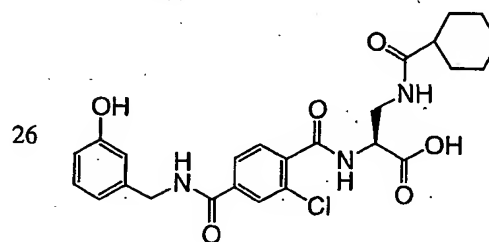
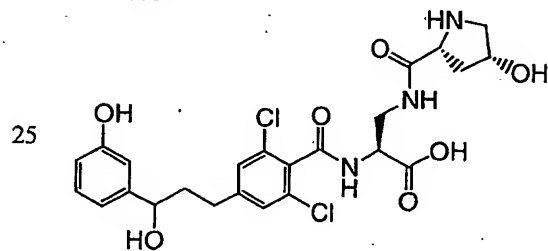
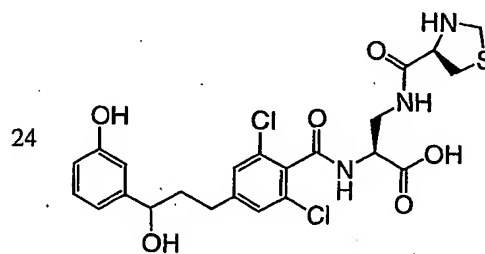
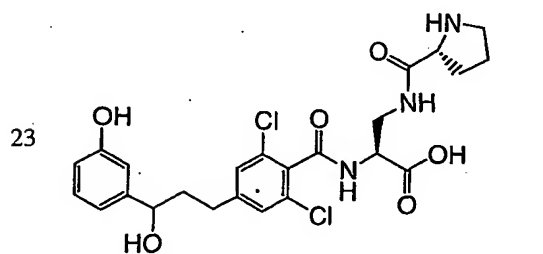
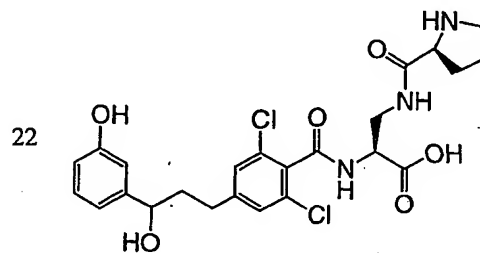
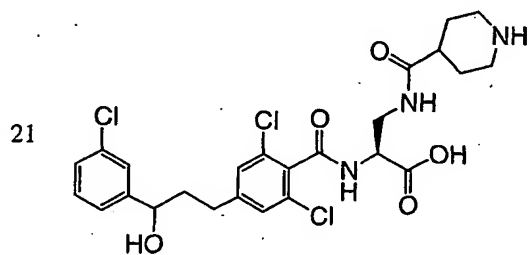
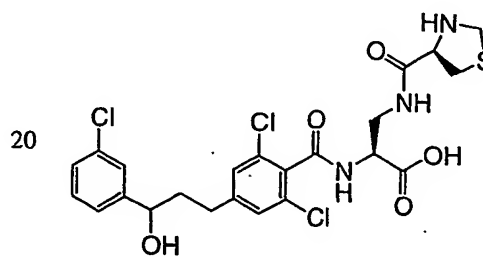
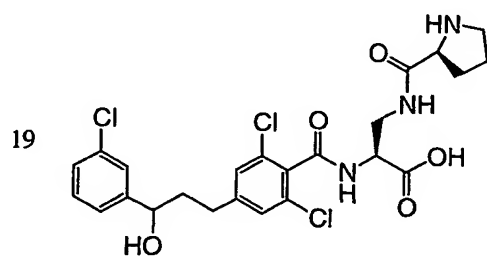
- 5 wherein Cy, Y, L and R<sub>1-6</sub> are as previously defined. In a particularly preferred embodiment, the carbon atom marked with an asterisk (\*) in compounds of formula (Ia) - (If) is chiral. In a particular embodiment, the carbon atom has an R-configuration. In another particular  
10 embodiment, the carbon atom has an S-configuration.

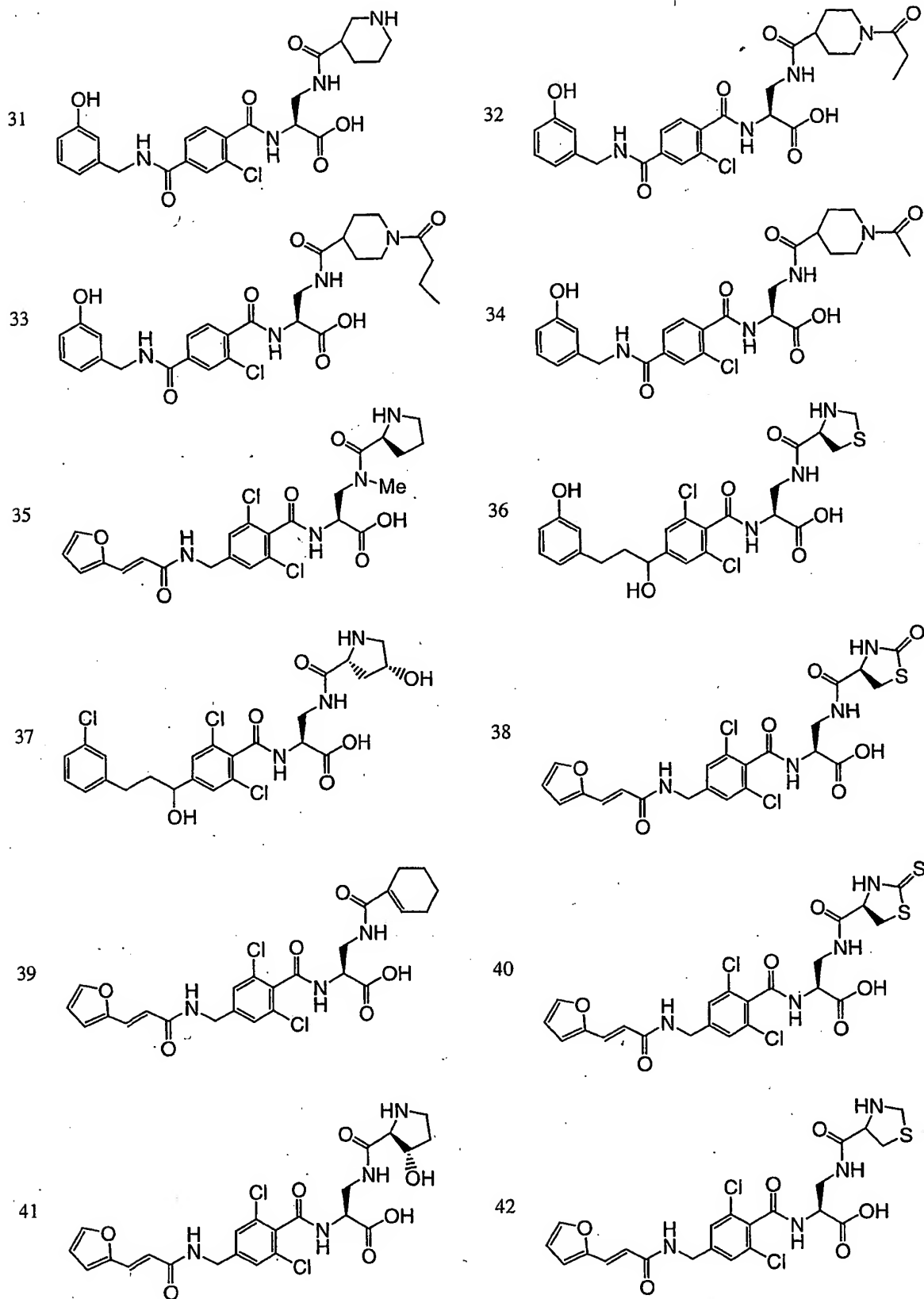
Particular compounds of the invention include:

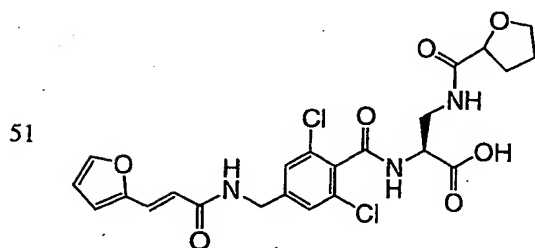
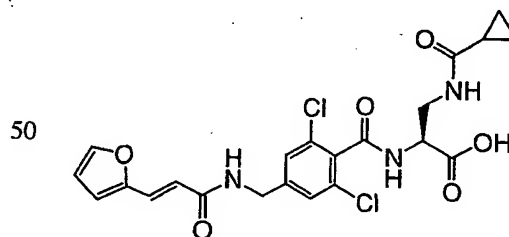
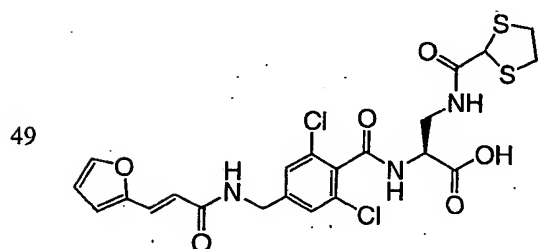
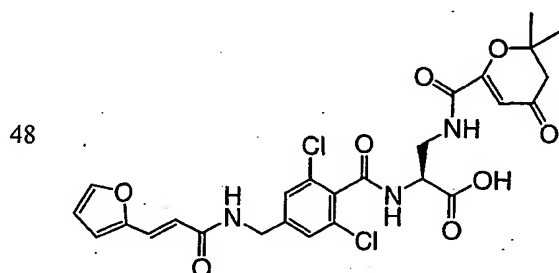
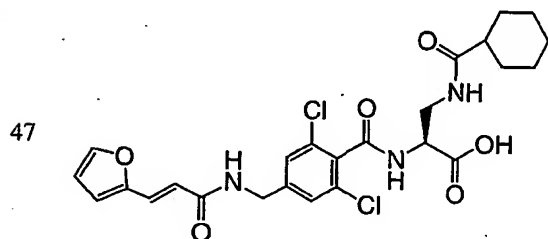
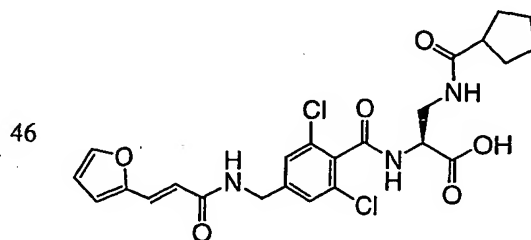
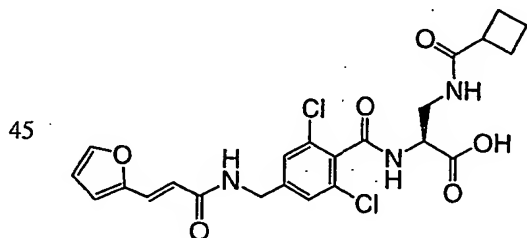
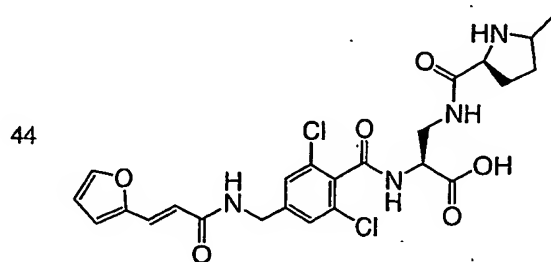
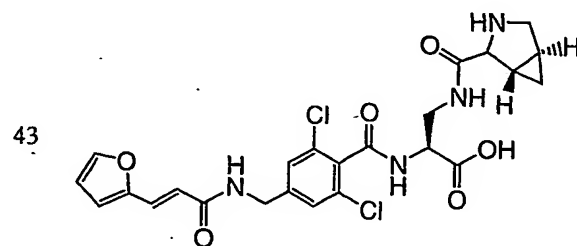












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and salts, solvates, hydrates and esters thereof.

10

It will be appreciated that compounds of the invention may incorporate chiral centers and therefore exist as geometric and stereoisomers. All such isomers are

5 contemplated and are within the scope of the invention  
whether in pure isomeric form or in mixtures of such  
isomers as well as racemates. Stereoisomeric compounds  
may be separated by established techniques in the art  
such as chromatography, i.e. chiral HPLC, or  
10 crystallization methods.

"Pharmaceutically acceptable" salts include both acid  
and base addition salts. Pharmaceutically acceptable  
acid addition salt refers to those salts which retain  
15 the biological effectiveness and properties of the free  
bases and which are not biologically or otherwise  
undesirable, formed with inorganic acids such as  
hydrochloric acid, hydrobromic acid, sulfuric acid,  
nitric acid, carbonic acid, phosphoric acid and the  
20 like, and organic acids may be selected from aliphatic,  
cycloaliphatic, aromatic, arylaliphatic, heterocyclic,  
carboxylic, and sulfonic classes of organic acids such  
as formic acid, acetic acid, propionic acid, glycolic  
acid, gluconic acid, lactic acid, pyruvic acid, oxalic  
25 acid, malic acid, maleic acid, malonic acid, succinic  
acid, fumaric acid, tartaric acid, citric acid, aspartic  
acid, ascorbic acid, glutamic acid, anthranilic acid,  
benzoic acid, cinnamic acid, mandelic acid, embonic  
acid, phenylacetic acid, methanesulfonic acid,  
30 ethanesulfonic acid, p-toluenesulfonic acid, salicylic  
acid and the like.

Pharmaceutically acceptable base addition salts include  
those derived from inorganic bases such as sodium,  
35 potassium, lithium, ammonium, calcium, magnesium, iron,  
zinc, copper, manganese, aluminum salts and the like.  
Particularly preferred are the ammonium, potassium,  
sodium, calcium and magnesium salts. Salts derived from

5 pharmaceutically acceptable organic nontoxic bases  
includes salts of primary, secondary, and tertiary  
amines, substituted amines including naturally occurring  
substituted amines, cyclic amines and basic ion exchange  
resins, such as isopropylamine, trimethylamine,  
10 diethylamine, triethylamine, tripropylamine,  
ethanolamine, 2-diethylaminoethanol, trimethamine,  
dicyclohexylamine, lysine, arginine, histidine,  
caffeine, procaine, hydrabamine, choline, betaine,  
ethylenediamine, glucosamine, methylglucamine,  
15 theobromine, purines, piperazine, piperidine, N-  
ethylpiperidine, polyamine resins and the like.  
Particularly preferred organic non-toxic bases are  
isopropylamine, diethylamine, ethanolamine,  
trimethamine, dicyclohexylamine, choline, and caffeine.

20  
Compounds of the invention may be prepared according to  
established organic synthesis techniques from starting  
materials and reagents that are commercially available or  
25 from starting materials that may be prepared from  
commercially available starting materials. Many standard  
chemical techniques and procedures are described in  
March, J., "Advanced Organic Chemistry" McGraw-Hill, New  
York, 1977; and Collman, J., "Principles and Applications  
30 of Organotransition Metal Chemistry" University Science,  
Mill Valley, 1987; and Larock, R., "Comprehensive Organic  
Transformations" Verlag, New York, 1989. It will be  
appreciated that depending on the particular substituents  
present on the compounds, suitable protection and  
35 deprotection procedures will be required in addition to  
those steps described herein. Numerous protecting groups  
are described in Greene and Wuts, Protective Groups in  
Organic Chemistry, 2d edition, John Wiley and Sons, 1991,

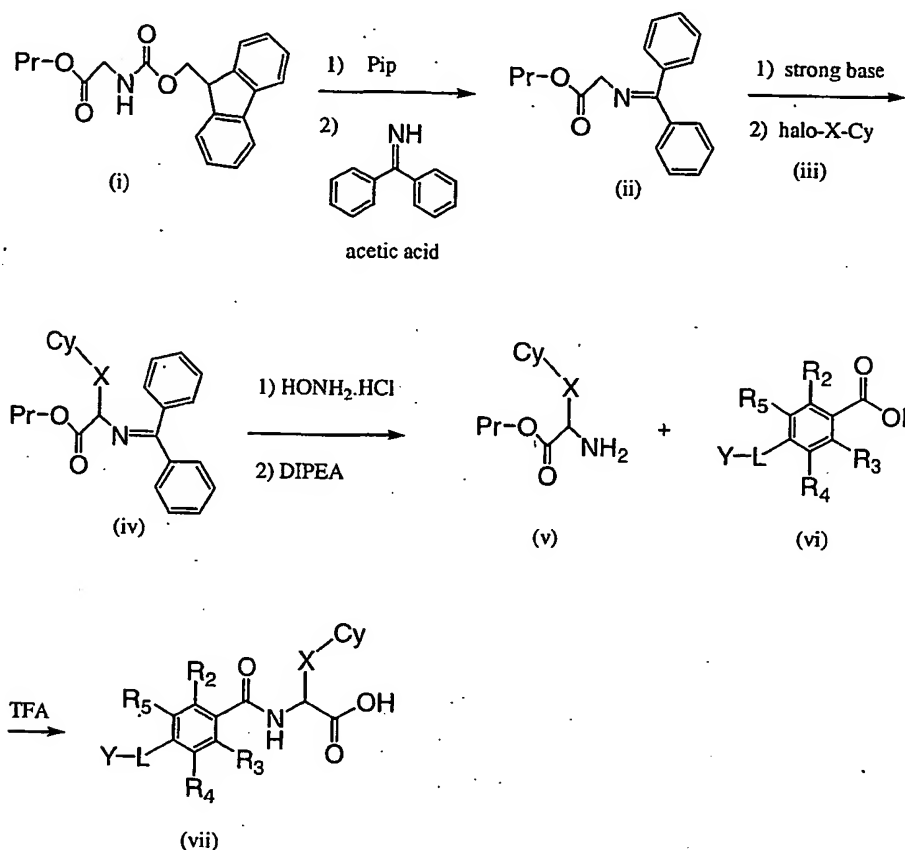
5 as well as detailed protection and deprotection  
procedures. For example, suitable amino protecting  
groups include t-butyloxycarbonyl (Boc), fluorenyl-  
methyloxycarbonyl (Fmoc), 2-trimethylsilyl-ethoxy-  
carbonyl (Teoc), 1-methyl-1-(4-biphenyl)ethoxycarbonyl  
10 (Bpoc), allyloxycarbonyl (Alloc), and benzyloxycarbonyl  
(Cbz). Carboxyl groups can be protected as fluorenyl-  
methyl groups, or alkyl esters i.e. methyl or ethyl, or  
alkenyl esters such as allyl. Hydroxyl groups may be  
protected with trityl, monomethoxytrityl, dimethoxy-  
15 trityl, and trimethoxytrityl groups.

Compounds may be prepared according to organic synthetic  
procedures described in United States patent application  
09/6446,330 filed on 14 September 2000, the entirety of  
20 which is incorporated herein by reference. Generally,  
compounds may be prepared according to reaction scheme 1.

25

5

Scheme 1



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Referring to scheme 1, a commercially available glycine amino acid residue is protected at the amino (e.g. fmoc) and carboxyl groups (Pr) or else immobilized on a solid support. The amino protecting group is removed with a suitable reagent and is reacted with diphenylketimine and subsequently alkylated at the alpha carbon with (iii) halo-X-Cy to give intermediate (vi). The imine (vi) is converted to the free amine (v) and then coupled with intermediate (vi) to provide the compound of the invention which is optionally deprotected at the carboxyl group to give free acid (vii). The free acid in turn may be esterified or amidated according to the definitions of substituent R<sub>1</sub>.

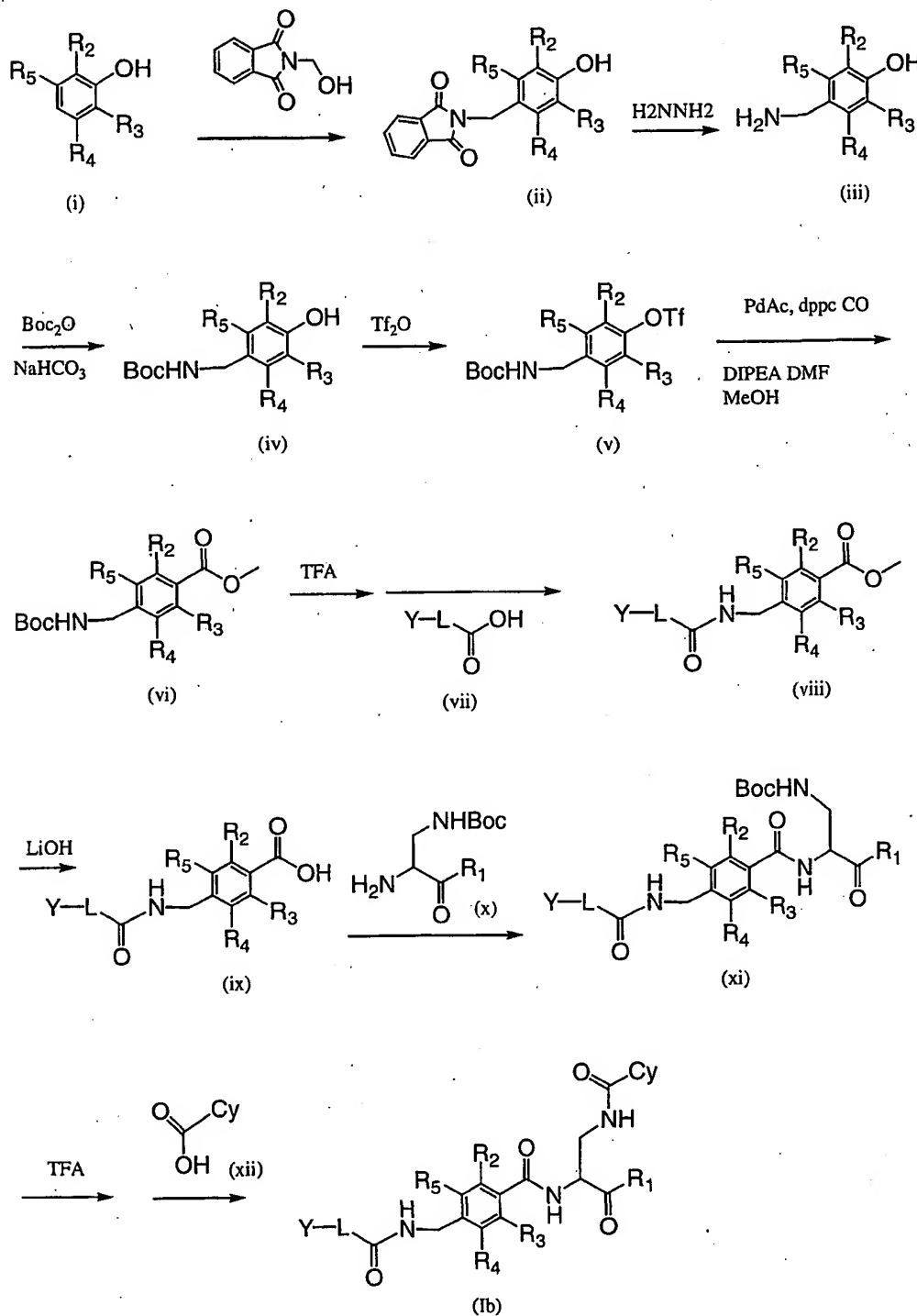


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In a particular embodiment, compounds of formula (Ib) of the invention may be prepared according to scheme 2.

Scheme 2

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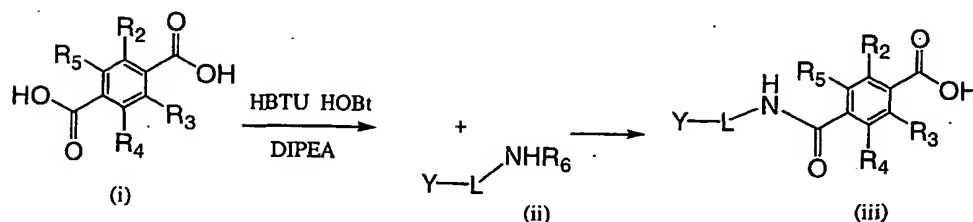


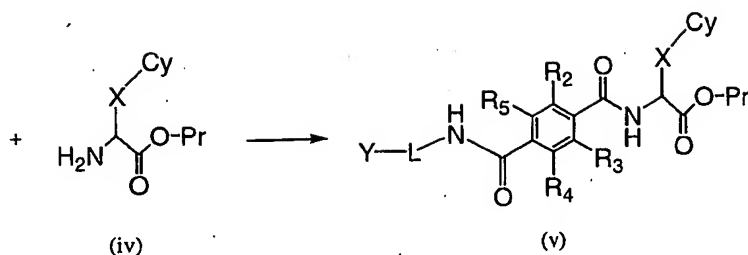
15

5 Referring to scheme 2, starting compound (i), commercially available or synthesized from commercially available reagents, is reacted with N-hydroxymethylphthalamide to give intermediate (ii) which is reacted with hydrazine to yield the free amine (iii).  
 10 The amine is Boc protected (iv) by reacting with Boc<sub>2</sub>O and sodiumbicarbonate and then reacted with triflic anhydride to give intermediate (v). The triflate intermediate (v) is then converted to the methyl ester intermediate (vi) by reacting with palladium(II) acetate and 1,3-bi(diphenylphosphino propane (dppp) and subsequently with diisopropyl ethylamine (DIPEA).  
 15 The Boc group of (vi) is removed with TFA and then reacted with carboxylic acid (vii) to give intermediate (viii). In a preferred embodiment of scheme 2, intermediate (vii) Y-L-C(O)OH is furylacrylic acid or thienylacrylic acid. The methyl ester of (viii) is removed with LiOH to give the free acid which is reacted with the N-Boc protected diaminopropanoic acid/ester (x) to yield intermediate (xi).  
 20 The Boc group of (xi) is removed with TFA and then reacted with carboxyl-substituted non-aromatic ring (xii) to give final compound (Ib) of the invention.

30 In another particular embodiment compounds of formula (Ic) of the invention may be prepared according to scheme 3.

Scheme 3





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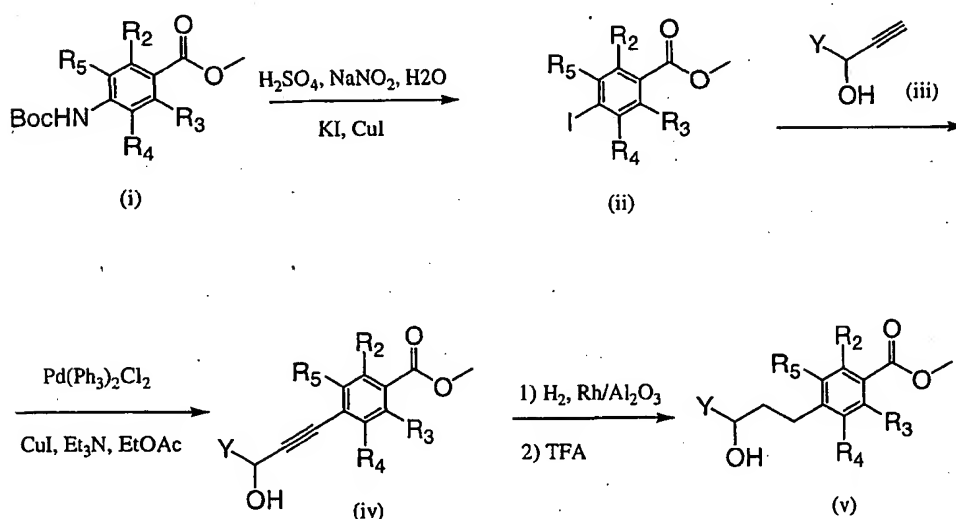
Referring to scheme 3, carboxylate starting reagent (i) is coupled with amine reagent (ii) Y-L-NHR<sub>6</sub> to give intermediate (iii) which is coupled with (iv) to yield compound of the invention (v). In a preferred embodiment of scheme 3, Y-L- is benzyl, optionally substituted with hydroxy, halogen, alkyl or alkoxy. More preferably Y-L- is 3-hydroxy-benzyl.

15

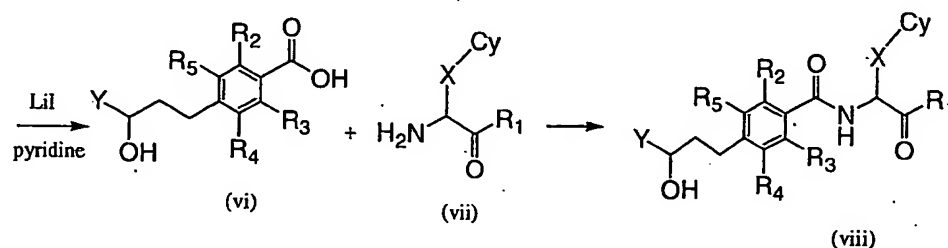
In another particular embodiment, compounds of formula (Id) of the invention may be prepared according to scheme 4.

20

Scheme 4



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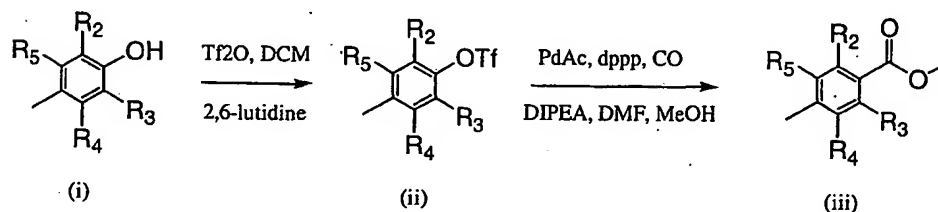


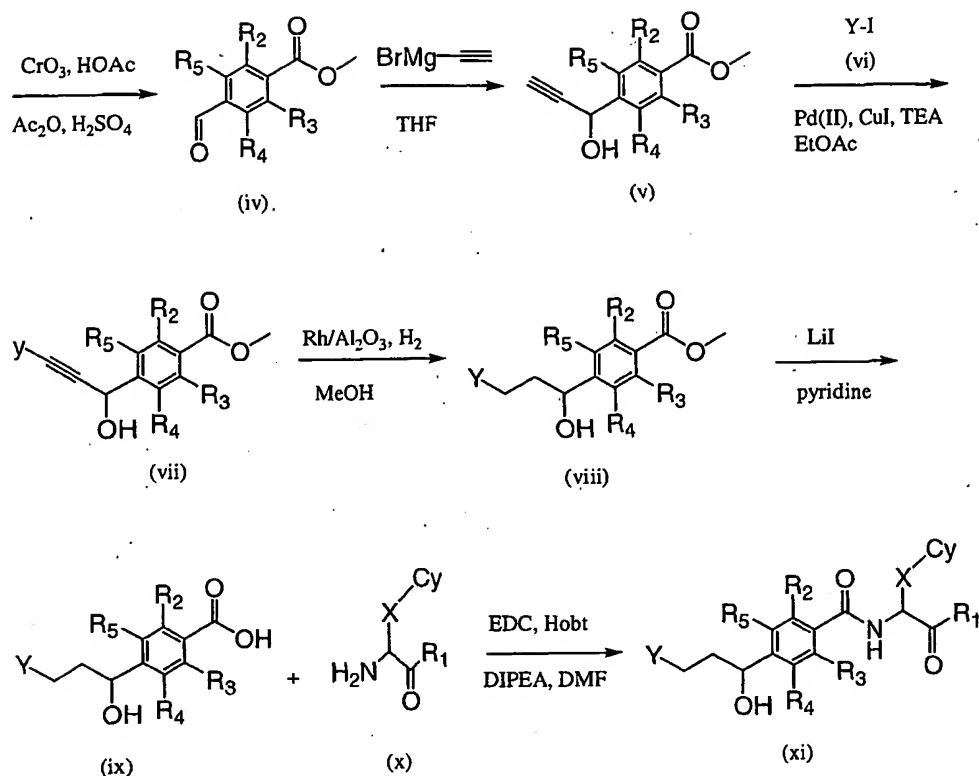
5

Referring to scheme 4, starting compound (i), prepared according to the procedures described in scheme 2, is converted to the iodo intermediate (ii) and reacted with alkyne (iii) to give intermediate (iv). Alkyne (iii) is prepared by reacting Y-COOH with Br-C≡CH in THF. Intermediate (iv) is then converted to the alkane (v) by reacting with Rh/Al<sub>2</sub>O<sub>3</sub> in H<sub>2</sub> atmosphere and the ester group converted to the free acid by reacting with LiI in pyridine to give (vi). Intermediate (vi) is reacted with amino acid (vii) to give compound of the invention (viii). In a particular embodiment of scheme 4, Y is phenyl optionally substituted with alkyl, hydroxy or halogen. In a particularly preferred embodiment Y is 3-chloro-phenyl or 3-hydroxy-phenyl.

In another particular embodiment, compounds of formula (Ie) of the invention may be prepared according to scheme 5.

Scheme 5





Referring to scheme 5, starting compound (i) is reacted with triflic anhydride and 2,6-lutidine to give intermediate (ii) which is converted to methyl ester (iii) by reacting with palladium(II)acetate, 1,3-bi(diphenylphosphino propane (dppp) and subsequently with diisopropyl ethylamine (DIPEA) in DMF and methanol. The ester (iii) is then reacted with  $\text{CrO}_3$  in acetic acid and anhydride to give aldehyde (iv) which is reacted with Grignard reagent ethynyl-magnesium bromide in THF to give alkyne intermediate (v). Iodo reagent (vi) Y-I is reacted with (v) to give intermediate (vii) which is converted to the alkane (viii) by reacting with  $\text{Rh/Al}_2\text{O}_3$  under hydrogen atmosphere. The methyl ester is converted to free acid (ix) with  $\text{LiI}$  in pyridine which is then coupled to amino acid residue (x) to give compound of the invention (xi). In preferred embodiments of scheme 5, Y is phenyl, optionally substituted with hydroxy, halogen,

alkyl or alkoxy. In more preferred embodiments, Y is 3-hydroxy-phenyl or 3-chloro-phenyl.

Compounds of the invention bind to LFA-1 preferentially over Mac-1. Accordingly, in an aspect of the invention, there is provided a method of inhibiting the binding of LFA-1 to ICAMs (cellular adhesion molecules), the method comprising contacting LFA-1 with a compound of formula (I). The method may be carried out in vivo or ex vivo as a solution based or cell based assay wherein the compound of the invention is introduced to LFA-1 in the presence of a putative or known ligand (such as ICAM-1). The compound of the invention may be labeled, for example isotopically radiolabeled, or labeled with a fluorophore such as fluorescein isothiocyanate (FITC), to facilitate detection of ligand binding or reduction thereof to the protease. Thus compounds of the invention are useful for diagnostic and screening assays.

5

Compounds of the invention are therapeutically and/or prophylactically useful for treating diseases or conditions mediated by LFA-1 activity. Accordingly in an aspect of the invention, there is provided a method of treating a disease or condition mediated by LFA-1 in a mammal, i.e. a human, comprising administering to said mammal an effective amount of a compound of the invention. By "effective amount" is meant an amount of compound which upon administration is capable of reducing the activity of LFA-1; or the amount of compound required to prevent, inhibit or reduce the severity of any symptom associated with an LFA-1 mediated condition or disease upon administration.

10

15

5 Compounds of the invention or compositions thereof are  
useful in treating conditions or diseases including:  
psoriasis; responses associated with inflammatory bowel  
disease (such as Crohn's disease and ulcerative colitis),  
dermatitis, meningitis, encephalitis, uveitis, allergic  
10 conditions such as eczema and asthma, conditions  
involving infiltration of T-cells and chronic  
inflammatory responses, skin hypersensitivity reactions  
(including poison ivy and poison oak); atherosclerosis,  
autoimmune diseases such as rheumatoid arthritis,  
15 systemic lupus erythematosus (SLE), diabetes mellitus,  
multiple sclerosis, Reynaud's syndrome, autoimmune  
thyroiditis, experimental autoimmune encephalomyelitis,  
Sjorgen's syndrome, juvenile onset diabetes, and immune  
responses associated with delayed hypersensitivity  
20 mediated by cytokines and T-lymphocytes typically found  
in tuberculosis, sarcoidosis, polymyositis,  
granulomatosis and vasculitis; pernicious anemia;  
diseases involving leukocyte diapedesis; CNS inflammatory  
disorder, multiple organ injury syndrome secondary to  
25 septicemia or trauma; autoimmune hemolytic anemia;  
myasthenia gravis; antigen-antibody complex mediated  
diseases; all types of transplantations, including graft  
vs. host or host vs. graft disease, HIV and rhinovirus  
infection, pulmonary fibrosis, alopecia, scleredema,  
30 endometriosis, vitiligo, ischemic reperfusion injury  
mediated by neutrophils such as acute myocardial  
infarction, restenosis following PTCA, invasive  
procedures such as cardiopulmonary bypass surgery,  
cerebral edema, stroke, traumatic brain injury,  
35 hemorrhagic shock, burns, ischemic kidney disease, multi-  
organ failure, wound healing and scar formation,  
atherosclerosis.

5     The actual amount of compound administered and the route  
of administration will depend upon the particular disease  
or condition as well as other factors such as the size,  
age, sex and ethnic origin of the individual being  
treated and is determined by routine analysis. In  
10    general, intravenous doses will be in the range from  
about 0.01-1000 mg/kg of patient body weight per day,  
preferably 0.1 to 20 mg/kg and more preferably 0.3 to 15  
mg/kg. Administration may be once or multiple times per  
day for several days, weeks or years or may be a few  
15    times per week for several weeks or years. The amount of  
compound administered by other routes will be that which  
provides a similar amount of compound in plasma compared  
to the intravenous amounts described which will take into  
consideration the plasma bioavailability of the  
20    particular compound administered.

In methods of the invention, the compound may be  
administered orally (including buccal, sublingual,  
inhalation), nasally, rectally, vaginally, intravenously  
25    (including intra-arterially), intradermally,  
subcutaneously, intramuscularly and topically. Compounds  
will be formulated into compositions suitable for  
administration for example with carriers, diluents,  
thickeners, adjuvants etc. as are routine in the  
30    formulation art. Accordingly, another aspect of the  
invention provides pharmaceutical compositions comprising  
a compound of formula (I) and a pharmaceutically  
acceptable carrier, excipient or adjuvant and may also  
include additional active ingredients such as anti-  
35    inflammatories e.g. NSAIDs.

Dosage forms include solutions, powders, tablets,  
capsules, gel capsules, suppositories, topical ointments



5 and creams and aerosols for inhalation. Formulations for  
non-parenteral administration may include sterile aqueous  
solutions which may also contain buffers, diluents and  
other suitable additives. Pharmaceutically acceptable  
10 organic or inorganic carrier substances suitable for non-  
parenteral administration which do not deleteriously  
react with compounds of the invention can be used.  
Suitable pharmaceutically acceptable carriers include,  
but are not limited to, water, salt solutions, alcohol,  
polyethylene glycols, gelatin, lactose, amylose,  
15 magnesium stearate, talc, silicic acid, viscous paraffin,  
hydroxymethylcellulose, polyvinylpyrrolidone and the  
like. The formulations can be sterilized and, if  
desired, mixed with auxiliary agents, e.g., lubricants,  
preservatives, stabilizers, wetting agents, emulsifiers,  
20 salts for influencing osmotic pressure, buffers,  
colorings flavorings and/or aromatic substances and the  
like which do not deleteriously react with compounds of  
the invention. Aqueous suspensions may contain  
substances which increase the viscosity of the suspension  
25 including, for example, sodium carboxymethylcellulose,  
sorbitol and/or dextran. Optionally, the suspension may  
also contain stabilizers.

Compounds of the invention exhibit high oral  
30 bioavailability. Accordingly, in a preferred embodiment,  
compounds of the invention are administered via oral  
delivery. Compositions for oral administration include  
powders or granules, suspensions or solutions in water or  
non-aqueous media, capsules, sachets, troches, tablets or  
35 SECs (soft elastic capsules or caplets). Thickeners,  
flavoring agents, diluents, emulsifiers, dispersing aids,  
carrier substances or binders may be desirably added to  
such formulations. Such formulations may be used to

5 effect delivering the compounds to the alimentary canal  
for exposure to the mucosa thereof. Accordingly, the  
formulation can consist of material effective in  
protecting the compound from pH extremes of the stomach,  
or in releasing the compound over time, to optimize the  
10 delivery thereof to a particular mucosal site. Enteric  
coatings for acid-resistant tablets, capsules and caplets  
are known in the art and typically include acetate  
phthalate, propylene glycol and sorbitan monoleate.

15 Various methods for producing formulations for alimentary  
delivery are well known in the art. See, generally  
*Remington's Pharmaceutical Sciences*, 18th Ed., Gennaro,  
ed., Mack Publishing Co., Easton, PA, 1990. The  
formulations of the invention can be converted in a known  
20 manner into the customary formulations, such as tablets,  
coated tablets, pills, granules, aerosols, syrups,  
emulsions, suspensions and solutions, using inert,  
non-toxic, pharmaceutically suitable excipients or  
solvents. The therapeutically active compound should in  
25 each case be present in a concentration of about 0.1% to  
about 99% by weight of the total mixture, that is to say  
in amounts which are sufficient to achieve the desired  
dosage range. The formulations are prepared, for  
example, by extending the active compounds with solvents  
30 and/or excipients, if appropriate using emulsifying  
agents and/or dispersing agents, and, for example, in the  
case where water is used as the diluent, organic solvents  
can be used as auxiliary solvents if appropriate.

35 Compositions may also be formulated with binding agents  
(e.g., pregelatinised maize starch, polyvinylpyrrolidone  
or hydroxypropyl methylcellulose); fillers (e.g.,  
lactose, microcrystalline cellulose or calcium hydrogen

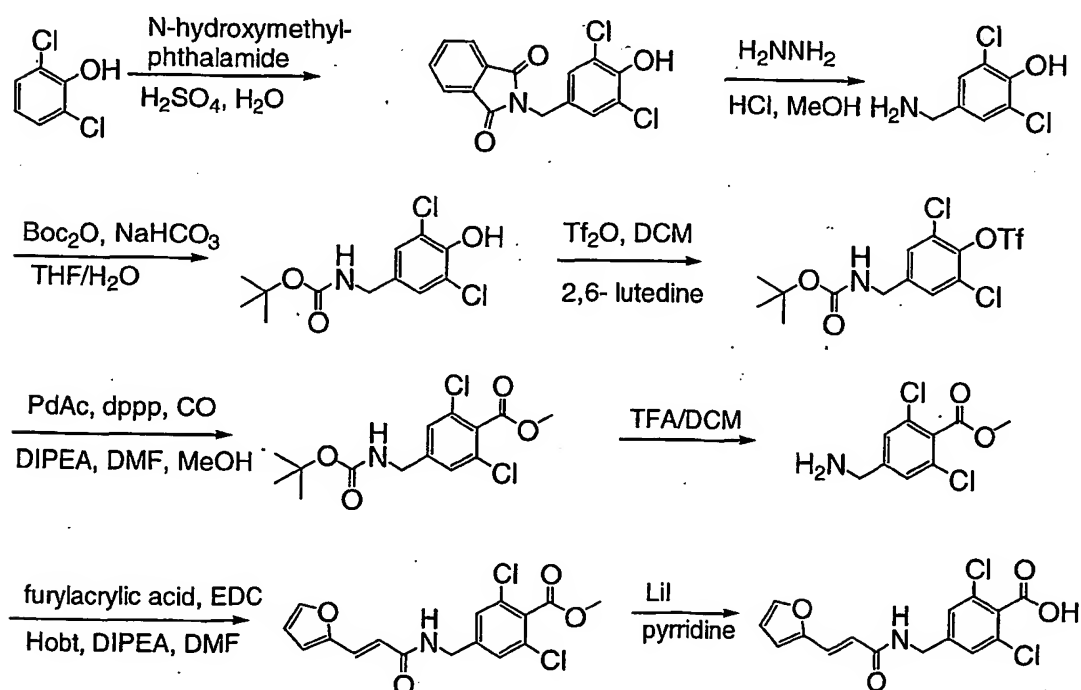
5     phosphate); lubricants (e.g., magnesium stearate, talc or  
silica); disintegrates (e.g., starch or sodium starch  
glycolate); or wetting agents (e.g., sodium lauryl  
sulfate). Tablets may be coated by methods well known in  
the art. The preparations may also contain flavoring,  
10     coloring and/or sweetening agents as appropriate.

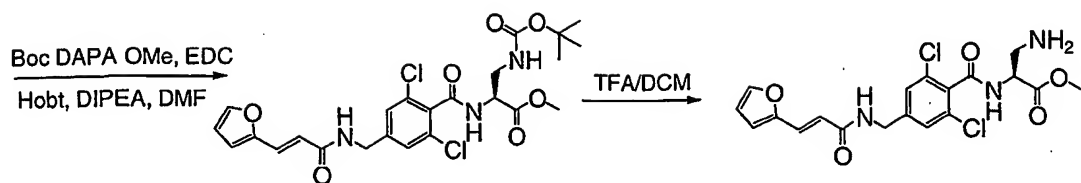
Formulations of the present invention suitable for oral  
administration may be presented as discrete units  
such as capsules, cachets or tablets each containing  
15     predetermined amounts of the active ingredients; as  
powders or granules; as solutions or suspensions in an  
aqueous liquid or a non-aqueous liquid; or as  
oil-in-water emulsions or water-in-oil liquid emulsions.  
A tablet may be made by compression or molding,  
20     optionally with one or more accessory ingredients.  
Compressed tablets may be prepared by compressing in a  
suitable machine, the active ingredients in a  
free-flowing form such as a powder or granules,  
optionally mixed with a binder, lubricant, inert diluent,  
25     preservative, surface active or dispersing agent. Molded  
tablets may be made by molding in a suitable machine a  
mixture of the powdered compound moistened with an inert  
liquid diluent. The tablets may optionally be coated or  
scored and may be formulated so as to provide slow or  
30     controlled release of the active ingredients therein.

## 5      EXAMPLES

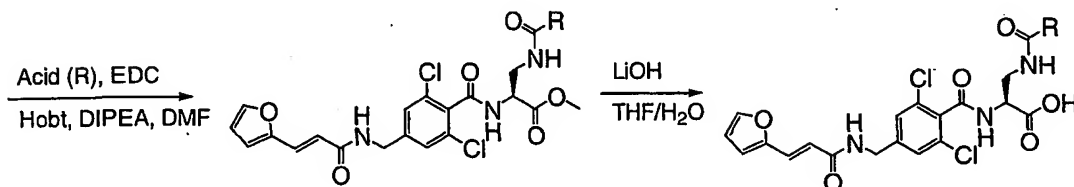
Abbreviations used in the following section: Boc = t-butylloxycarbonyl; Boc<sub>2</sub>O = t-butylloxycarbonyl anhydride; DMA = dimethylacetimide; DMF = dimethylformamide; Hobt = 1-hydroxybenztriazole; TFA = trifluoroacetic acid; DCM = dichloromethane; MeOH = methanol; HOAc = acetic acid; HCl = hydrochloric acid; H<sub>2</sub>SO<sub>4</sub> = sulfuric acid; K<sub>2</sub>CO<sub>3</sub> = potassium carbonate; THF = tetrahydrofuran; EtOAc = ethyl acetate; DIPEA = diisopropylethylamine; NaHCO<sub>3</sub> = sodium bicarbonate; ACN = acetonitrile; Na<sub>2</sub>•EDTA = ethylenediaminetetraacetic acid sodium salt; TBAF = tetrabutyl ammonium fluoride; EDC = 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide•HCl; TEA = triethylamine; MgSO<sub>4</sub> = magnesium sulfate; TES = triethylsilane; Et<sub>2</sub>O = diethyl ether; BBr<sub>3</sub> = boron tribromide

EXAMPLE 1      Synthesis of compounds 16, 17, 38-40, 46-50





5



A round bottom flask was equipped with an efficient overhead stirrer and charged with concentrated H<sub>2</sub>SO<sub>4</sub> (2.7 x volume of H<sub>2</sub>O) and H<sub>2</sub>O and cooled to ~-5°C with an ethanol/ice bath. Once cool, 1 equivalent 2,6 dichloro phenol and 1 equivalent of N-(hydroxymethyl)phthalimide were added with vigorous stirring. The reaction was kept cool for 4 hours and then allowed to warm to room temperature overnight with constant stirring. The reaction generally proceeded to a point where there was just a solid in the round bottom flask. At that point EtOAc and H<sub>2</sub>O were added and stirred into the solid. Large chunks were broken up and then the precipitate was filtered and washed with more EtOAc and H<sub>2</sub>O. The product was then used without further purification after drying overnight under vacuum.

1 equivalent of the dry product and methanol (22.5ml x #g of starting material) was added to a round bottom flask equipped with a H<sub>2</sub>O condenser and stirring bar. 1.2 equivalents of hydrazine mono hydrate was added and the mixture refluxed for 4 hours. After cooling to room temperature, concentrated HCl (4.5ml x #g of starting material) was carefully added. Upon completion of the addition, the mixture was refluxed overnight (> 8 hours).

5       The reaction was cooled to 0°C and the precipitated by-product was removed by filtration. The filtrate was then concentrated *in vacuo*.

10       The crude amine residue was dissolved in a 3:2 THF/H<sub>2</sub>O solution. 1.1 equivalents of solid NaHCO<sub>3</sub> and 1.1 equivalents of Boc<sub>2</sub>O were added and the mixture was stirred overnight. The reaction was concentrated, and the residue was partitioned between H<sub>2</sub>O and Et<sub>2</sub>O. The aqueous layer was extracted with Et<sub>2</sub>O and the combined organic  
15       layers were dried over MgSO<sub>4</sub> and concentrated *in vacuo* to a solid. Recrystallization from hot methanol and H<sub>2</sub>O provided pure product.

20       1 equivalent of the Boc protected amine and 1.5 equivalents of 2, 6- lutidine was dissolved, with mild heating when necessary, in DCM in a round bottom flask. Once the starting material had completely dissolved, the mixture was cooled to -78°C under N<sub>2</sub> with a dry ice ethanol bath. Once cool, 2.5 equivalents of triflic  
25       anhydride was added and the reaction was allowed to slowly come to room temperature with stirring. The reaction was monitored by TLC and was generally done in 4 hours. Upon completion, the reaction was concentrated *in vacuo* and the residue partitioned between EtOAc and H<sub>2</sub>O.  
30       The organic layer was washed twice with 0.1N H<sub>2</sub>SO<sub>4</sub>, twice with saturated NaHCO<sub>3</sub>, once with brine, dried over MgSO<sub>4</sub> and concentrated *in vacuo*. The residue was then purified on silica gel using DCM as eluent to provide pure triflate.

35

1 equivalent of triflate was dissolved in DMF and MeOH in the glass insert of a high pressure Parr bomb. The starting material was then degassed while stirring with

5 CO for 10 minutes. 0.15 equivalents palladium(II) acetate  
and 0.15 equivalents of 1, 3- bis(diphenylphosphino)  
propane were then added and the mixture was then degassed  
while stirring with CO for another 10 minutes at which  
time 2.5 equivalents of diisopropyl ethyl amine was  
10 added. After properly assembling the bomb, it was charged  
with 300psi CO gas and heated to 70°C with stirring  
overnight. The bomb was then cooled and vented. The  
mixture was transferred to a round bottom flask and  
concentrated *in vacuo*. The residue was then purified on  
15 silica gel using DCM with 1% acetone and 1% TEA as eluent  
to provide pure methyl ester.

The Boc protected amine was dissolved in a solution of  
TFA in DCM (1:1). After 20 minutes, the reaction was  
20 concentrated *in vacuo*. The resulting oil was dissolved in  
toluene and then reconcentrated *in vacuo*. The TFA salt of  
the amine was dissolved in Et<sub>2</sub>O and washed twice with a  
10% solution of K<sub>2</sub>CO<sub>3</sub> in H<sub>2</sub>O and once with brine. The  
organic layer was then dried over MgSO<sub>4</sub>, filtered and  
25 concentrated *in vacuo*.

1 equivalent of the free based amine, 3 equivalents of  
furylacrylic acid, 3 equivalents of EDC and 1 equivalent  
of Hobt were dissolved DMA. The reaction was stirred at  
30 room temperature and monitored by TLC (9/1 DCM/MeOH).  
Upon completion, the mixture was concentrated *in vacuo*.  
The resulting oil was re suspended in Et<sub>2</sub>O and washed  
twice with 0.1 N H<sub>2</sub>SO<sub>4</sub>, twice with saturated NaHCO<sub>3</sub>, and  
once with brine. The organic layer was then dried over  
35 MgSO<sub>4</sub>, filtered and concentrated *in vacuo*. The residue was  
then purified on silica gel using 5% methanol in DCM as  
eluent to provide pure methyl ester.

5        2.3 equivalents of lithium iodide was added to 1  
equivalent of the methyl ester in pyridine, and the  
mixture heated at reflux for 8 hours. The reaction was  
concentrated *in vacuo* and the residue was partitioned  
between EtOAc and 1N HCl. The aqueous layer was extracted  
10       three times with EtOAc, and the combined organic layers  
were washed with 1M NaHCO<sub>3</sub>, dried over MgSO<sub>4</sub> and  
concentrated *in vacuo*. The residue was dissolved in NMM  
and the solution concentrated *in vacuo*. The residue was  
taken up in DCM and then washed three times with 1N HCl.  
15       The organic layer was dried over MgSO<sub>4</sub> and concentrated *in*  
*vacuo* to provide the benzoic acid in high enough purity  
to be used without further purification.

1        1 equivalent of the acid, 2 equivalents of commercially  
20       available  $\beta$ - Boc- diaminopropionic acid methyl ester, 2  
equivalents of EDC, 1 equivalent of Hobt and 3  
equivalents of DIPEA were dissolved DMA. The reaction was  
stirred at room temperature and monitored by TLC (9/1  
DCM/MeOH). Upon completion, the mixture was concentrated  
25       in *vacuo*. The resulting oil was re suspended in Et<sub>2</sub>O and  
washed twice with 0.1 N H<sub>2</sub>SO<sub>4</sub>, twice with saturated  
NaHCO<sub>3</sub>, and once with brine. The organic layer was then  
dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo*. The  
residue was then purified on silica gel using 5% methanol  
30       in DCM as eluent to provide pure methyl ester.

The Boc protected amine was dissolved in a solution of  
TFA in DCM (1:1). After 20 minutes, the reaction was  
concentrated *in vacuo*. The resulting oil was dissolved in  
35       toluene and then reconcentrated *in vacuo*. 1 equivalent of  
this amine, 2 equivalents of the appropriate commercially  
available carboxylic acid (compound 16, N- acetyl-D-  
proline; compound 17, N- acetyl-L-proline; compound 38,



5 (-)-2-oxo-4-thiazolidinecarboxylic acid; compound 39, 1-cyclohexene-1-carboxylic acid; compound 40, (4R)-(-)-2-thio-4-thiazolidinecarboxylic acid; compound 45, cyclobutanecarboxylic acid; compound 46, cyclopentanecarboxylic acid; compound 47, cyclohexanecarboxylic acid; compound 48, 3,4-dihydro-2,2-dimethyl-4-oxo-2H-pyran-6-carboxylic acid; compound 49, ethyl 1,3-dithiolane-2-carboxylate (2 equivalents of the ethyl ester was saponified with 3 equivalents of LiOH·H<sub>2</sub>O in THF/H<sub>2</sub>O (3/1) The reaction was monitored by TLC (9/1 DCM/MeOH). Upon completion, the mixture was acidified to pH 2 with 1M HCl and then concentrated in vacuo. The resulting solid was used without further purification); compound 50, cyclopropanecarboxylic acid; compound 51, tetrahydro-2-furoic acid), 2 equivalents of EDC, 1 equivalent of HOBt and 3 equivalents of DIPEA were dissolved in DMA. The reaction was stirred at room temperature and monitored by TLC (9/1 DCM/MeOH). Upon completion, the mixture was concentrated in vacuo. The resulting oil was re suspended in Et<sub>2</sub>O and washed twice with 0.1 N H<sub>2</sub>SO<sub>4</sub>, twice with saturated NaHCO<sub>3</sub>, and once with brine. The organic layer was then dried over MgSO<sub>4</sub>, filtered and concentrated in vacuo. The residue was then purified on silica gel using 5% methanol in DCM as eluent to provide pure methyl ester.

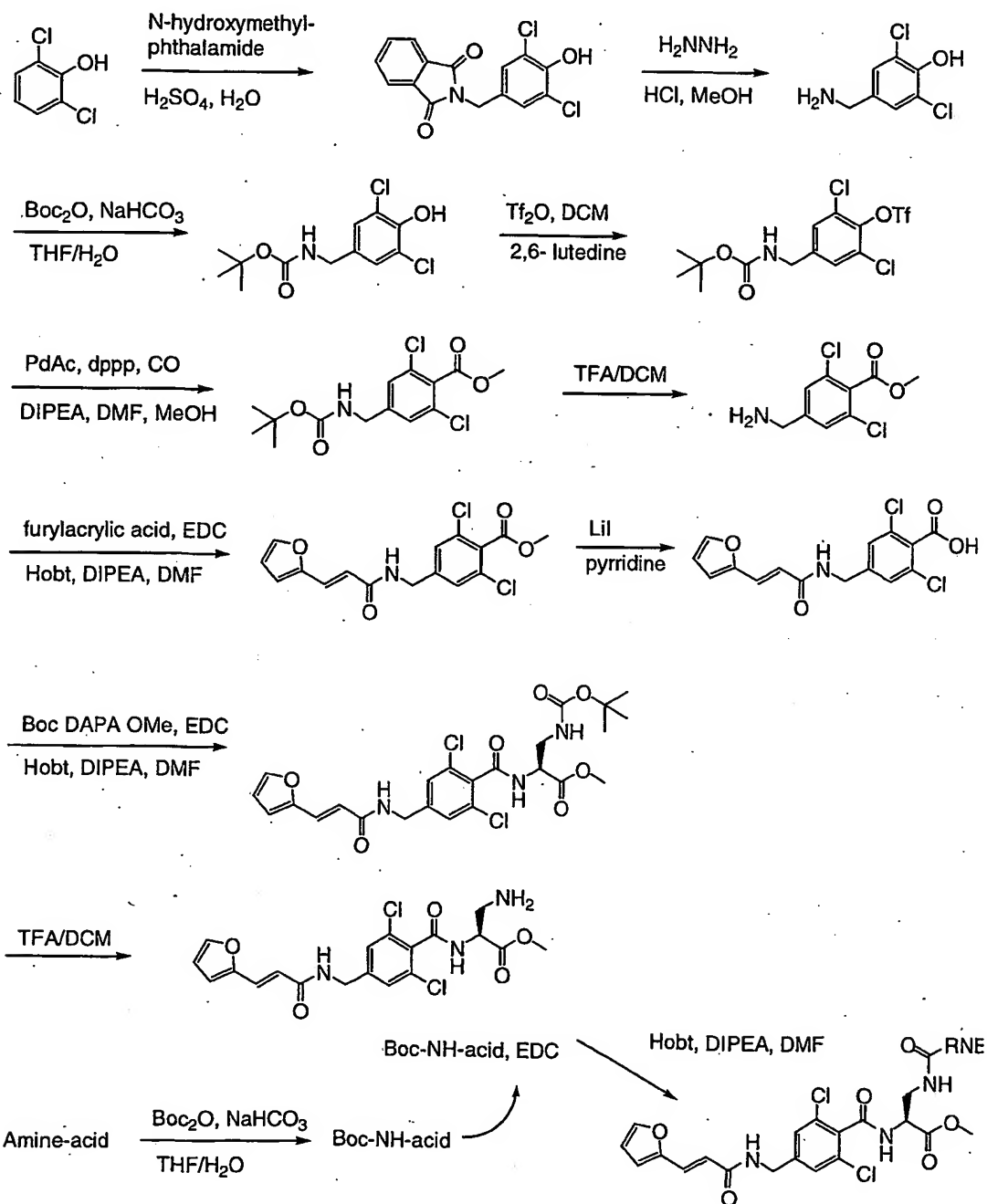
30 1 equivalent of the resultant methyl ester was dissolved in THF/H<sub>2</sub>O (3/1) and 3 equivalents of LiOH·H<sub>2</sub>O was added. The reaction was monitored by TLC (9/1 DCM/MeOH). Upon completion, the mixture was acidified to pH 2 with 1M HCl and then concentrated in vacuo. The resulting solid was re suspended in Et<sub>2</sub>O and washed twice with 0.1 M HCl and once with brine. The organic layer was then dried over MgSO<sub>4</sub>, filtered and concentrated in vacuo. The resulting

35

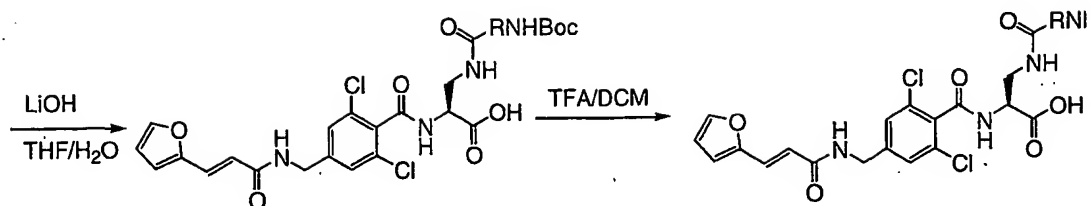
5 acid was then purified by reverse phase HPLC, verified by  
electrospray mass spectrometry and lyophilized to a  
powder.

10

# EXAMPLE 2 Synthesis of compounds 1-15, 41, 43



15



5

A round bottom flask was equipped with an efficient overhead stirrer and charged with concentrated H<sub>2</sub>SO<sub>4</sub> (2.7 x volume of H<sub>2</sub>O) and H<sub>2</sub>O and cooled to ~-5°C with an ethanol/ice bath. Once cool, 1 equivalent 2,6 dichloro phenol and 1 equivalent of N-(hydroxymethyl)phthalimide were added with vigorous stirring. The reaction was kept cool for 4 hours and then allowed to warm to room temperature overnight with constant stirring. The reaction generally proceeds to a point where there was just a solid in the round bottom flask. At this point EtOAc and H<sub>2</sub>O were added and stirred into the solid. Large chunks were broken up and then the precipitate was filtered and washed with more EtOAc and H<sub>2</sub>O. The product was then used without further purification after drying overnight under vacuum.

1 equivalent of the dry product and methanol (22.5ml x #g of starting material) was added to a round bottom flask equipped with a H<sub>2</sub>O condenser and stirring bar. 1.2 equivalents of hydrazine mono hydrate was added and the mixture refluxed for 4 hours. After cooling to room temperature, concentrated HCl (4.5ml x #g of starting material) was carefully added. Upon completion of the addition, the mixture was refluxed overnight (> 8 hours). The reaction was cooled to 0°C and the precipitated by-product was removed by filtration. The filtrate was then concentrated *in vacuo*.

5       The crude amine residue was dissolved in a 3:2 THF/H<sub>2</sub>O solution. 1.1 equivalents of solid NaHCO<sub>3</sub> and 1.1 equivalents of Boc<sub>2</sub>O were added and the mixture was stirred overnight. The reaction was concentrated, and the residue was partitioned between H<sub>2</sub>O and Et<sub>2</sub>O. The aqueous  
10       layer was extracted with Et<sub>2</sub>O and the combined organic layers were dried over MgSO<sub>4</sub> and concentrated *in vacuo* to a solid. Recrystallization from hot methanol and H<sub>2</sub>O provided pure product.

15       1 equivalent of the Boc protected amine and 1.5 equivalents of 2, 6- lutidine was dissolved, with mild heating when necessary, in DCM in a round bottom flask. Once the starting material had completely dissolved, the mixture was cooled to -78°C under N<sub>2</sub> with a dry ice  
20       ethanol bath. Once cool, 2.5 equivalents of triflic anhydride was added and the reaction was allowed to slowly come to room temperature with stirring. The reaction was monitored by TLC and was generally done in 4 hours. Upon completion, the reaction was concentrated *in vacuo* and the residue partitioned between EtOAc and H<sub>2</sub>O.  
25       The organic layer was washed twice with 0.1N H<sub>2</sub>SO<sub>4</sub>, twice with saturated NaHCO<sub>3</sub>, once with brine, dried over MgSO<sub>4</sub> and concentrated *in vacuo*. The residue was then purified on silica gel using DCM as eluent to provide pure  
30       triflate.

1 equivalent of triflate was dissolved in DMF and MeOH in the glass insert of a high pressure Parr bomb. The starting material was then degassed while stirring with  
35       CO for 10 minutes. 0.15 equivalents palladium(II) acetate and 0.15 equivalents of 1, 3- bis(diphenylphosphino) propane were then added and the mixture was then degassed while stirring with CO for another 10 minutes at which

5     time 2.5 equivalents of diisopropyl ethyl amine was added. After properly assembling the bomb, it was charged with 300psi CO gas and heated to 70°C with stirring overnight. The bomb was then cooled and vented. The mixture was transferred to a round bottom flask and  
10     concentrated in vacuo. The residue was then purified on silica gel using DCM with 1% acetone and 1% TEA as eluent to provide pure methyl ester.

The Boc protected amine was dissolved in a solution of  
15     TFA in DCM (1:1). After 20 minutes, the reaction was concentrated in vacuo. The resulting oil was dissolved in toluene and then reconcentrated in vacuo. The TFA salt of the amine was dissolved in Et<sub>2</sub>O and washed twice with a 10% solution of K<sub>2</sub>CO<sub>3</sub> in H<sub>2</sub>O and once with brine. The  
20     organic layer was then dried over MgSO<sub>4</sub>, filtered and concentrated in vacuo.

1 equivalent of the free based amine, 3 equivalents of furylacrylic acid, 3 equivalents of EDC and 1 equivalent  
25     of Hobt were dissolved DMA. The reaction was stirred at room temperature and monitored by TLC (9/1 DCM/MeOH). Upon completion, the mixture was concentrated in vacuo. The resulting oil was re suspended in Et<sub>2</sub>O and washed twice with 0.1 N H<sub>2</sub>SO<sub>4</sub>, twice with saturated NaHCO<sub>3</sub>, and  
30     once with brine. The organic layer was then dried over MgSO<sub>4</sub>, filtered and concentrated in vacuo. The residue was then purified on silica gel using 5% methanol in DCM as eluent to provide pure methyl ester.

35     2.3 equivalents of lithium iodide was added to 1 equivalent of the methyl ester in pyridine, and the mixture heated at reflux for 8 hours. The reaction was concentrated in vacuo and the residue was partitioned

5        between EtOAc and 1N HCl. The aqueous layer was extracted  
three times with EtOAc, and the combined organic layers  
were washed with 1M NaHCO<sub>3</sub>, dried over MgSO<sub>4</sub> and  
concentrated *in vacuo*. The residue was dissolved in NMM  
and the solution concentrated *in vacuo*. The residue was  
10       taken up in DCM and then washed three times with 1N HCl.  
The organic layer was dried over MgSO<sub>4</sub> and concentrated *in vacuo*  
to provide the benzoic acid in high enough purity  
to be used without further purification.

15       1 equivalent of the acid, 2 equivalents of commercially  
available  $\beta$ -Boc-, diaminopropionic acid methyl ester, 2  
equivalents of EDC, 1 equivalent of Hobt and 3  
equivalents of DIPEA were dissolved DMA. The reaction was  
stirred at room temperature and monitored by TLC (9/1  
20       DCM/MeOH). Upon completion, the mixture was concentrated  
*in vacuo*. The resulting oil was re suspended in Et<sub>2</sub>O and  
washed twice with 0.1 N H<sub>2</sub>SO<sub>4</sub>, twice with saturated  
NaHCO<sub>3</sub>, and once with brine. The organic layer was then  
dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo*. The  
25       residue was then purified on silica gel using 5% methanol  
in DCM as eluent to provide pure methyl ester.

The Boc protected amine was dissolved in a solution of  
TFA in DCM (1:1). After 20 minutes, the reaction was  
30       concentrated *in vacuo*. The resulting oil was dissolved in  
toluene and then reconcentrated *in vacuo*. 1 equivalent of  
this amine, 2 equivalents of the appropriate commercially  
available carboxylic acid ((N-Boc acids were purchased  
where available. Other acids were purchased as the free  
35       amine and Boc protected by the following procedure: The  
amine was dissolved in a 3:2 THF/H<sub>2</sub>O solution. 1.1  
equivalents of solid NaHCO<sub>3</sub> and 1.1 equivalents of Boc<sub>2</sub>O  
were added and the mixture was stirred overnight. The

5 reaction was concentrated to remove the THF, and the resulting aqueous layer was partitioned with hexanes. The aqueous layer was then acidified to pH 2 with 1N HCl and then partitioned twice with EtOAc. The combined organic layers were dried over  $\text{MgSO}_4$  and concentrated in vacuo.

10 The resulting product was used without further purification) compound 1 D,L-pipecolinic acid; compound 2, nipecotic acid; compound 3, isonipecotic acid; compound 4, N-Boc-L-proline; compound 5, N-Boc-D-proline; compound 6, Boc-L-thiazolidine-4-carboxylic acid;

15 compound 7, N-Boc-L-pyroglutamic acid; compound 8, N-Boc-D-pyroglutamic acid; compound 9, L-pipecolinic acid; compound 10, D-cis-4-hydroxyproline; compound 11, L-cis-4-hydroxyproline; compound 12, D-hydroxyproline; compound 13, (2S, 3S)-3-methylpyrrolidine-2-carboxylic acid;

20 compound 14, N-Boc-L-hydroxyproline; compound 15, Boc-D-thiazolidine-4-carboxylic acid; compound 41, L-3-hydroxyproline; compound 43, trans-3-azabicyclo[3.1.0]hexane-2-carboxylic acid), 2 equivalents of EDC, 1 equivalent of Hobt and 3 equivalents of DIPEA were dissolved DMA. The reaction was stirred at room

25 temperature and monitored by TLC (9/1 DCM/MeOH). Upon completion, the mixture was concentrated in vacuo. The resulting oil was re suspended in  $\text{Et}_2\text{O}$  and washed twice with 0.1 N  $\text{H}_2\text{SO}_4$ , twice with saturated  $\text{NaHCO}_3$ , and once

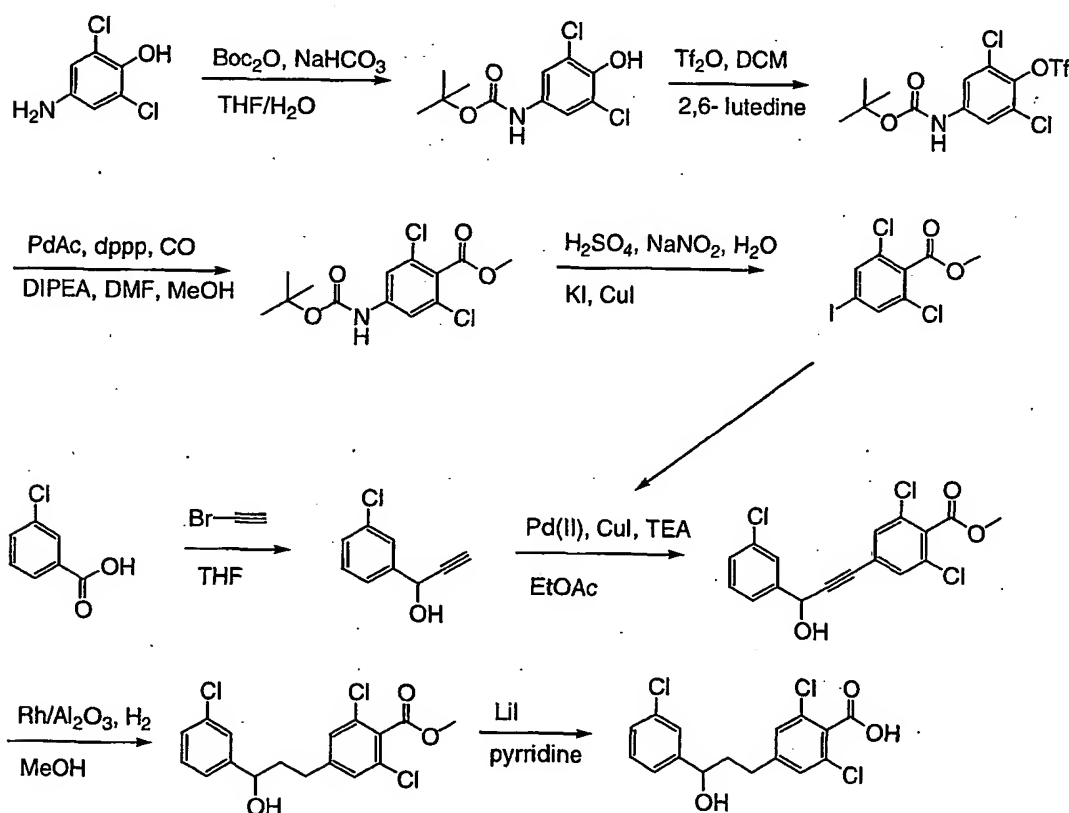
30 with brine. The organic layer was then dried over  $\text{MgSO}_4$ , filtered and concentrated in vacuo. The residue was then purified on silica gel using 5% methanol in DCM as eluent to provide pure methyl ester.

35 1 equivalent of the resultant methyl ester was dissolved in THF/ $\text{H}_2\text{O}$  (3/1) and 3 equivalents of  $\text{LiOH}\cdot\text{H}_2\text{O}$  was added. The reaction was monitored by TLC (9/1 DCM/MeOH). Upon completion, the mixture was acidified to pH 2 with 1M HCl

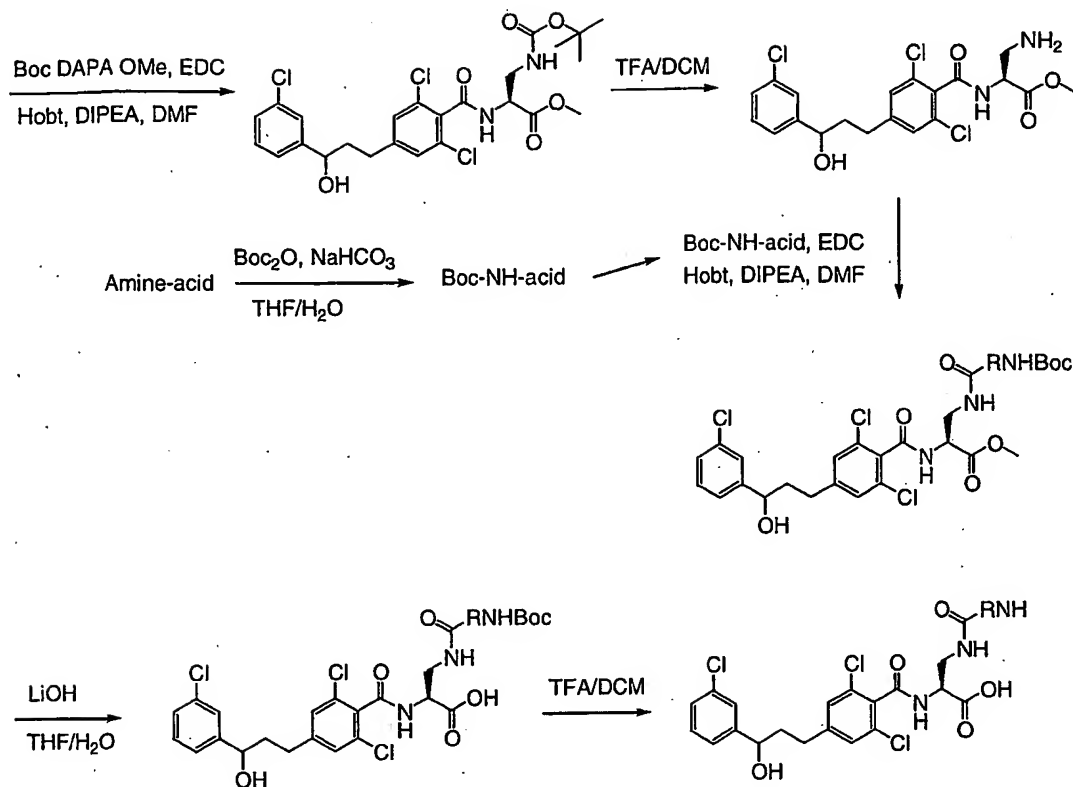
5 and then concentrated *in vacuo*. The resulting solid was re suspended in Et<sub>2</sub>O and washed twice with 0.1 M HCl and once with brine. The organic layer was then dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo*.

10 Where appropriate the Boc protected residue was dissolved in a solution of TFA in DCM (1:1). After 20 minutes, the reaction was concentrated *in vacuo*. The resulting oil was dissolved in toluene and then re-concentrated *in vacuo*. The resulting acid was then purified by reverse phase  
15 HPLC, verified by electrospray mass spectrometry and lyophilized to a powder.

20 EXAMPLE 3 Synthesis of compounds 18-21







5

10 1 equivalent of 4-amino-2,6-dichlorophenol was dissolved in a 3:2 THF/H<sub>2</sub>O solution. 1.1 equivalents of solid NaHCO<sub>3</sub> and 1.1 equivalents of Boc<sub>2</sub>O were added and the solution was stirred overnight. The reaction was concentrated, and the residue was partitioned between H<sub>2</sub>O and Et<sub>2</sub>O. The

15 aqueous layer was extracted with Et<sub>2</sub>O and the combined organic layers were dried over MgSO<sub>4</sub> and concentrated in vacuo to a solid. Recrystallization out of Et<sub>2</sub>O/hexane provided pure product.

20 1 equivalent of the phenol was dissolved in DCM containing 2.6 equivalents of 2, 6-lutidine and the mixture was cooled to -78°C. After adding 1.25 equivalents of triflic anhydride the stirring reaction was allowed to warm to room temperature overnight. The

25 reaction was then concentrated, and the residue was partitioned between Et<sub>2</sub>O and H<sub>2</sub>O. The aqueous layer was

- 5        extracted with  $\text{Et}_2\text{O}$  and the combined organic layers were dried over  $\text{MgSO}_4$  and concentrated *in vacuo*. The residue was purified by silica gel flash chromatography (9:1 hexane/ $\text{Et}_2\text{O}$ ) to provide the pure triflate.
- 10       To a stirring solution of 1 equivalent of the triflate in a 2/1 mixture of DMF/MeOH was added 0.15 equivalents of 1, 3-bis(diphenylphosphino)-propane and 2.5 equivalents of TEA. Carbon monoxide gas was bubbled through this solution for 15 minutes, then 0.15 equivalents of
- 15        $\text{Pd}(\text{OAc})_2$  was added and the reaction was stirred at  $70^\circ\text{C}$  for 5-7 hours under an atmosphere of CO (using a balloon filled with CO). The reaction was then concentrated *in vacuo*, and the residue was partitioned between  $\text{Et}_2\text{O}$  and  $\text{H}_2\text{O}$ . The aqueous layer was extracted twice with  $\text{Et}_2\text{O}$  and
- 20       the combined organic layers were dried over  $\text{MgSO}_4$ , filtered through a plug of silica gel and concentrated *in vacuo*. The residue was purified by silica gel flash chromatography (9:1:0.02 hexane/DCM/ $\text{Et}_2\text{O}$ ) to provide the pure methyl ester.
- 25       1 equivalent of the Boc-aniline was dissolved in methanol and the solution saturated with HCl. The reaction was heated at  $50^\circ\text{C}$  for 3h, then concentrated *in vacuo*. The pale yellow solid was heated in 35%  $\text{H}_2\text{SO}_4$  until complete
- 30       dissolution occurred. Upon cooling the mixture by the addition of ice  $\text{H}_2\text{O}$  the amine bisulfate precipitated. The reaction flask was cooled in an ice bath and the mixture stirred vigorously while 1.1 equivalents of sodium nitrite in  $\text{H}_2\text{O}$  was added drop wise. The reaction was
- 35       stirred at  $0^\circ\text{C}$  for another 1.5 hours. An aqueous solution of 10 equivalents of KI was added, followed immediately with 17 equivalents CuI. The reaction was stirred at room temperature for 14 hours, then extracted 3 times with

5 Et<sub>2</sub>O. The combined organic layers were washed with 1M NaHCO<sub>3</sub>, brine, and dried over MgSO<sub>4</sub>, then concentrated in vacuo. The residue was purified by silica gel flash chromatography (95:5 hexane/Et<sub>2</sub>O) to provide the pure aryl iodide methyl ester.

10

A solution of 1 equivalent of 3-Chlorobenzaldehyde in THF was cooled to -78°C and 1.1 equivalents of 0.5M ethynylmagnesium bromide/THF was added. After stirring the reaction at room temperature for 3 hours, it was  
15 diluted with Et<sub>2</sub>O and washed twice with 10% citric acid. The combined aqueous layers were back-extracted once with Et<sub>2</sub>O. The combined organic layers were washed twice with saturated aqueous NaHCO<sub>3</sub>, dried over MgSO<sub>4</sub> and concentrated in vacuo. The residue was purified by silica  
20 gel flash chromatography (4:1 to 3:2 hexane/Et<sub>2</sub>O) to provide the pure alkyne.

1 equivalent of the aryl iodide methyl ester was dissolved in EtOAc and the solution was degassed by  
25 passing N<sub>2</sub> through a pipette and into the solution for 10 minutes. 1.25 equivalents of the alkyne was added, followed by 0.02 equivalents of dichlorobis(triphenylphosphine)palladium(II), 0.04  
equivalents of CuI and 5 equivalents TEA. The reaction  
30 was stirred for 14 hours, diluted with EtOAc, washed twice with 5% Na<sub>2</sub>•EDTA, brine and then dried over MgSO<sub>4</sub> and concentrated in vacuo. The residue was purified by silica gel flash chromatography (gradient elution, using Et<sub>2</sub>O to EtOAc) to provide the pure aryl alkyne.

35

1 equivalent of the aryl alkyne was dissolved in MeOH and the solution was degassed by passing N<sub>2</sub> through a pipette and into the solution for 10 minutes. The 5% Rh/Al<sub>2</sub>O<sub>3</sub> was

5     added, one balloon-full of hydrogen was passed through  
the solution, and the reaction was stirred under an  
atmosphere of  $H_2$  (using a balloon) for 7 hours, after  
which the reaction was filtered through a pad of celite  
and concentrated in *vacuo*. The residue was purified by  
10     silica gel flash chromatography (gradient elution, using  
 $Et_2O$  to  $EtOAc$ ) to provide the pure product.

2.3 equivalents of lithium iodide was added to 1  
equivalent of the methyl ester in pyridine, and the  
15     mixture heated at reflux for 8 hours. The reaction was  
concentrated in *vacuo* and the residue was partitioned  
between  $EtOAc$  and 1N  $HCl$ . The aqueous layer was extracted  
three times with  $EtOAc$ , and the combined organic layers  
were washed with 1M  $NaHCO_3$ , dried over  $MgSO_4$  and  
20     concentrated in *vacuo*. The residue was dissolved in NMM  
and the solution concentrated in *vacuo*. The residue was  
taken up in DCM and then washed three times with 1N  $HCl$ .  
The organic layer was dried over  $MgSO_4$  and concentrated in  
*vacuo* to provide the benzoic acid in high enough purity  
25     to be used without further purification.

1 equivalent of the acid, 2 equivalents of commercially  
available  $\beta$ -Boc-diaminopropionic acid methyl ester, 2  
equivalents of EDC, 1 equivalent of Hobt and 3  
30     equivalents of DIPEA were dissolved DMA. The reaction was  
stirred at room temperature and monitored by TLC (9/1  
DCM/ $MeOH$ ). Upon completion, the mixture was concentrated  
in *vacuo*. The resulting oil was re suspended in  $Et_2O$  and  
washed twice with 0.1 N  $H_2SO_4$ , twice with saturated  
35      $NaHCO_3$ , and once with brine. The organic layer was then  
dried over  $MgSO_4$ , filtered and concentrated in *vacuo*. The  
residue was then purified on silica gel using 5% methanol  
in DCM as eluent to provide pure methyl ester.

5

The Boc protected amine was dissolved in a solution of TFA in DCM (1:1). After 20 minutes, the reaction was concentrated *in vacuo*. The resulting oil was dissolved in toluene and then reconcentrated *in vacuo*. 1 equivalent of this amine, 2 equivalents of the appropriate commercially available carboxylic acid ((N-Boc acids were purchased where available. Other acids were purchased as the free amine and Boc protected by the following procedure: The amine was dissolved in a 3:2 THF/H<sub>2</sub>O solution. 1.1 equivalents of solid NaHCO<sub>3</sub> and 1.1 equivalents of Boc<sub>2</sub>O were added and the mixture was stirred overnight. The reaction was concentrated to remove the THF, and the resulting aqueous layer was partitioned with hexanes. The aqueous layer was then acidified to pH 2 with 1N HCl and then partitioned twice with EtOAc. The combined organic layers were dried over MgSO<sub>4</sub> and concentrated *in vacuo*. The resulting product was used without further purification) example 18, N-Boc-D-proline; example 19, N-Boc-L-proline; example 20, Boc-L-thiazolidine-4-carboxylic acid; example 21, isonipecotic acid; 2 equivalents of EDC, 1 equivalent of Hobt and 3 equivalents of DIPEA were dissolved DMA. The reaction was stirred at room temperature and monitored by TLC (9/1 DCM/MeOH). Upon completion, the mixture was concentrated *in vacuo*. The resulting oil was re suspended in Et<sub>2</sub>O and washed twice with 0.1 N H<sub>2</sub>SO<sub>4</sub>, twice with saturated NaHCO<sub>3</sub>, and once with brine. The organic layer was then dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo*. The residue was then purified on silica gel using 5% methanol in DCM as eluent to provide pure methyl ester.

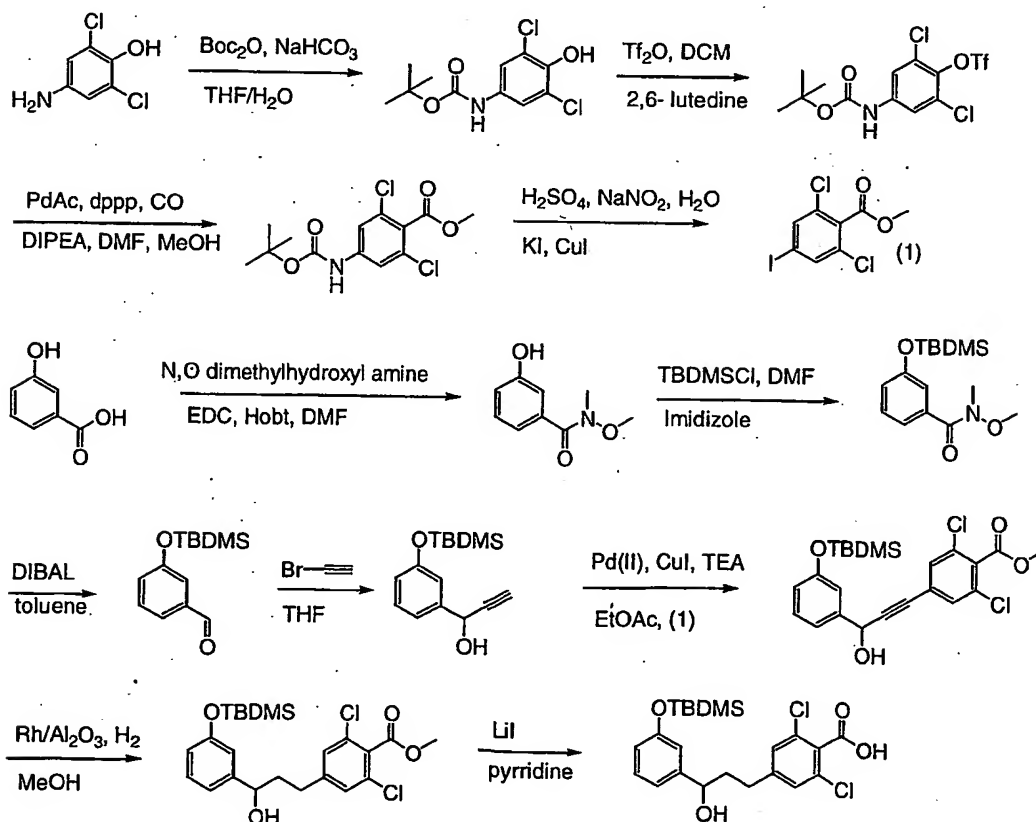
1 equivalent of the resultant methyl ester was dissolved in THF/H<sub>2</sub>O (3/1) and 3 equivalents of LiOH·H<sub>2</sub>O was added.

5 The reaction was monitored by TLC (9/1 DCM/MeOH). Upon completion, the mixture was acidified to pH 2 with 1M HCl and then concentrated *in vacuo*. The resulting solid was re suspended in Et<sub>2</sub>O and washed twice with 0.1 M HCl and once with brine. The organic layer was then dried over  
 10 MgSO<sub>4</sub>, filtered and concentrated *in vacuo*.

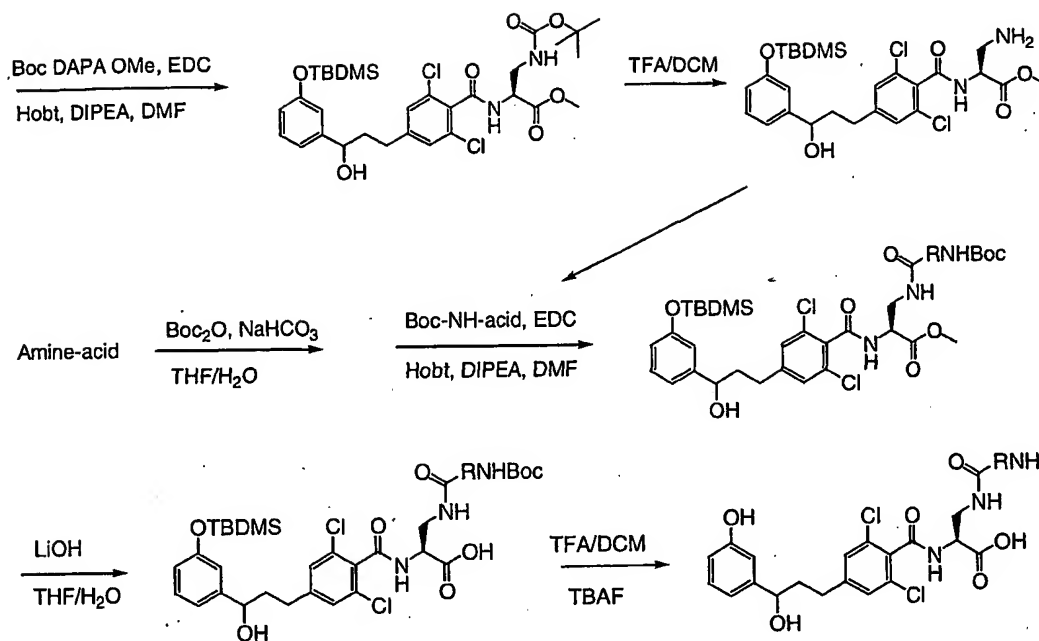
The Boc protected residue was dissolved in a solution of TFA in DCM (1:1). After 20 minutes, the reaction was concentrated *in vacuo*. The resulting oil was dissolved in  
 15 toluene and then reconcentrated *in vacuo*. The resulting acid was then purified by reverse phase HPLC, verified by electrospray mass spectrometry and lyophilized to a powder.

20

#### EXAMPLE 4 Synthesis of compounds 22-25



25



5

1 equivalent of 4-amino-2, 6-dichlorophenol was dissolved in a 3:2 THF/ $\text{H}_2\text{O}$  solution. 1.1 equivalents of solid  $\text{NaHCO}_3$  and 1.1 equivalents of  $\text{Boc}_2\text{O}$  were added and the solution was stirred overnight. The reaction was concentrated, and the residue was partitioned between  $\text{H}_2\text{O}$  and  $\text{Et}_2\text{O}$ . The aqueous layer was extracted with  $\text{Et}_2\text{O}$  and the combined organic layers were dried over  $\text{MgSO}_4$  and concentrated in vacuo to a solid. Recrystallization out of  $\text{Et}_2\text{O}$ /hexane provided pure product.

15

1 equivalent of the phenol was dissolved in DCM containing 2.6 equivalents of 2, 6-lutidine and the mixture was cooled to  $-78^\circ\text{C}$ . After adding 1.25 equivalents of triflic anhydride the stirring reaction was allowed to warm to room temperature overnight. The reaction was then concentrated, and the residue was partitioned between  $\text{Et}_2\text{O}$  and  $\text{H}_2\text{O}$ . The aqueous layer was extracted with  $\text{Et}_2\text{O}$  and the combined organic layers were dried over  $\text{MgSO}_4$  and concentrated in vacuo. The residue

25

5 was purified by silica gel flash chromatography (9:1 hexane/Et<sub>2</sub>O) to provide the pure triflate.

To a stirring solution of 1 equivalent of the triflate in a 2/1 mixture of DMF/MeOH was added 0.15 equivalents of  
10 1, 3-bis(diphenylphosphino)-propane and 2.5 equivalents of TEA. Carbon monoxide gas was bubbled through this solution for 15 minutes, then 0.15 equivalents of Pd(OAc)<sub>2</sub> was added and the reaction was stirred at 70°C for 5-7 hours under an atmosphere of CO (using a balloon  
15 filled with CO). The reaction was then concentrated *in vacuo*, and the residue was partitioned between Et<sub>2</sub>O and H<sub>2</sub>O. The aqueous layer was extracted twice with Et<sub>2</sub>O and the combined organic layers were dried over MgSO<sub>4</sub>, filtered through a plug of silica gel and concentrated *in vacuo*.  
20 The residue was purified by silica gel flash chromatography (9:1:0.02 hexane/DCM/Et<sub>2</sub>O) to provide the pure methyl ester.

1 equivalent of the Boc-aniline was dissolved in methanol and the solution saturated with HCl. The reaction was  
25 heated at 50°C for 3h, then concentrated *in vacuo*. The pale yellow solid was heated in 35% H<sub>2</sub>SO<sub>4</sub> until complete dissolution occurred. Upon cooling the mixture by the addition of ice H<sub>2</sub>O the amine bisulfate precipitated. The  
30 reaction flask was cooled in an ice bath and the mixture stirred vigorously while 1.1 equivalents of sodium nitrite in H<sub>2</sub>O was added drop wise. The reaction was stirred at 0°C for another 1.5 hours. An aqueous solution of 10 equivalents of KI was added, followed immediately  
35 with 17 equivalents CuI. The reaction was stirred at room temperature for 14 hours, then extracted 3 times with Et<sub>2</sub>O. The combined organic layers were washed with 1M NaHCO<sub>3</sub>, brine, and dried over MgSO<sub>4</sub>, then concentrated *in*



5 vacuo. The residue was purified by silica gel flash chromatography (95:5 hexane/Et<sub>2</sub>O) to provide the pure aryl iodide methyl ester.

1.3 equivalents of DIPEA was added to a heterogeneous  
10 mixture of 1 equivalent of 3-hydroxybenzoic acid, 1.3 equivalents of N, O-dimethylhydroxylamine hydrochloride, 1.3 equivalents of HOBt and 1.3 equivalents of EDC stirring in DMF. All solids eventually dissolved as the mixture was stirred at room temperature for 28 hours.  
15 After concentrating the mixture, the residue was partitioned between Et<sub>2</sub>O and H<sub>2</sub>O. The aqueous layer was extracted three times with Et<sub>2</sub>O and the combined organic layers were dried over MgSO<sub>4</sub>, and concentrated *in vacuo*. The residue was purified by silica gel flash  
20 chromatography (Et<sub>2</sub>O) to provide the pure hydroxamate.

1 equivalent of the hydroxamate, 2.2 equivalents of *t*-butyldimethyl silyl chloride and 3 equivalents of imidazole were dissolved in DMF and stirred at room  
25 temperature. The reaction was monitored by TLC (9/1 DCM/MeOH). Upon reaction completion, the mixture was concentrated *in vacuo*. The resulting oil was re suspended in Et<sub>2</sub>O and washed twice with saturated NaHCO<sub>3</sub>, and once with brine. The organic layer was then dried over MgSO<sub>4</sub>,  
30 filtered and concentrated *in vacuo*. The product was then used with out further purification.

To a stirred -78°C solution of 1 equivalent of the protected hydroxamate in THF was added a solution of 1.2  
35 equivalents of 1.5 M DIBAL in toluene drop wise. The reaction mixture was stirred for an additional 3 hours at -78°C or until TLC showed clean formation of product, with only a trace of starting material. The reaction was

5 quenched by adding to a separatory funnel containing Et<sub>2</sub>O and 0.35M NaHSO<sub>4</sub>. The layers were separated. The aqueous layer was extracted three times with ethyl ether. The combined organic layers were washed twice with 1N HCl, saturated aqueous NaHCO<sub>3</sub>, and over MgSO<sub>4</sub>, filtered through  
10 a plug of silica gel, and concentrated in vacuo. No further purification of the aldehyde was necessary.

A solution of 1 equivalent of the protected aldehyde in THF was cooled to -78°C and 1.1 equivalents of 0.5M  
15 ethynylmagnesium bromide/THF was added. After stirring the reaction at room temperature for 3 hours, it was diluted with Et<sub>2</sub>O and washed twice with 10% citric acid. The combined aqueous layers were back-extracted once with Et<sub>2</sub>O. The combined organic layers were washed twice with  
20 saturated aqueous NaHCO<sub>3</sub>, dried over MgSO<sub>4</sub> and concentrated in vacuo. The residue was purified by silica gel flash chromatography (4:1 to 3:2 hexane/Et<sub>2</sub>O) to provide the pure alkyne.

25 1 equivalent of the aryl iodide methyl ester was dissolved in EtOAc and the solution was degassed by passing N<sub>2</sub> through a pipette and into the solution for 10 minutes. 1.25 equivalents of the alkyne was added, followed by 0.02 equivalents of  
30 dichlorobis(triphenylphosphine)palladium(II), 0.04 equivalents of CuI and 5 equivalents TEA. The reaction was stirred for 14 hours, diluted with EtOAc, washed twice with 5% Na<sub>2</sub>•EDTA, brine and then dried over MgSO<sub>4</sub> and concentrated in vacuo. The residue was purified by  
35 silica gel flash chromatography (gradient elution, using Et<sub>2</sub>O to EtOAc) to provide the pure aryl alkyne.

5 1 equivalent of the aryl alkyne was dissolved in MeOH and the solution was degassed by passing N<sub>2</sub> through a pipette and into the solution for 10 minutes. The 5% Rh/Al<sub>2</sub>O<sub>3</sub> was added, one balloon-full of hydrogen was passed through the solution, and the reaction was stirred under an  
10 atmosphere of H<sub>2</sub> (using a balloon) for 7 hours, after which the reaction was filtered through a pad of celite and concentrated in vacuo. The residue was purified by silica gel flash chromatography (gradient elution, using Et<sub>2</sub>O to EtOAc) to provide the pure product.

15 2.3 equivalents of lithium iodide was added to 1 equivalent of the methyl ester in pyridine, and the mixture heated at reflux for 8 hours. The reaction was concentrated in vacuo and the residue was partitioned  
20 between EtOAc and 1N HCl. The aqueous layer was extracted three times with EtOAc, and the combined organic layers were washed with 1M NaHCO<sub>3</sub>, dried over MgSO<sub>4</sub> and concentrated in vacuo. The residue was dissolved in NMM and the solution concentrated in vacuo. The residue was  
25 taken up in DCM and then washed three times with 1N HCl. The organic layer was dried over MgSO<sub>4</sub> and concentrated in vacuo to provide the benzoic acid in high enough purity to be used without further purification.

30 1 equivalent of the acid, 2 equivalents of commercially available β- Boc- diaminopropionic acid methyl ester, 2 equivalents of EDC, 1 equivalent of Hobt and 3 equivalents of DIPEA were dissolved DMA. The reaction was stirred at room temperature and monitored by TLC (9/1  
35 DCM/MeOH). Upon completion, the mixture was concentrated in vacuo. The resulting oil was re suspended in Et<sub>2</sub>O and washed twice with 0.1 N H<sub>2</sub>SO<sub>4</sub>, twice with saturated NaHCO<sub>3</sub>, and once with brine. The organic layer was then

5       dried over  $\text{MgSO}_4$ , filtered and concentrated *in vacuo*. The residue was then purified on silica gel using 5% methanol in DCM as eluent to provide pure methyl ester.

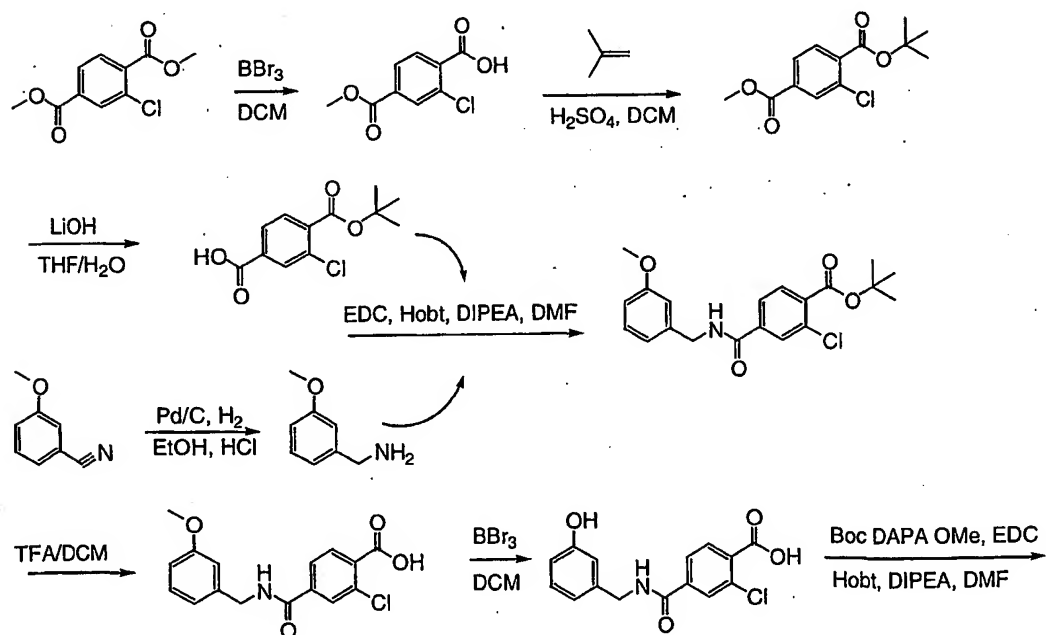
10       The Boc protected amine was dissolved in a solution of TFA in DCM (1:1). After 20 minutes, the reaction was concentrated *in vacuo*. The resulting oil was dissolved in toluene and then reconcentrated *in vacuo*. 1 equivalent of this amine, 2 equivalents of the appropriate commercially available carboxylic acid ((N-Boc acids were purchased where available. Other acids were purchased as the free amine and Boc protected by the following procedure: The amine was dissolved in a 3:2 THF/ $\text{H}_2\text{O}$  solution. 1.1 equivalents of solid  $\text{NaHCO}_3$  and 1.1 equivalents of  $\text{Boc}_2\text{O}$  were added and the mixture was stirred overnight. The reaction was concentrated to remove the THF, and the resulting aqueous layer was partitioned with hexanes. The aqueous layer was then acidified to pH 2 with 1N HCl and then partitioned twice with EtOAc. The combined organic layers were dried over  $\text{MgSO}_4$  and concentrated *in vacuo*. The resulting product was used without further purification) example 22, N-Boc-L-proline; example 23, N-Boc-D-proline; example 24, Boc-L-thiazolidine-4-carboxylic acid; example 25, D-hydroxy proline; 2 equivalents of EDC, 1 equivalent of Hobt and 3 equivalents of DIPEA were dissolved DMA. The reaction was stirred at room temperature and monitored by TLC (9/1 DCM/MeOH). Upon completion, the mixture was concentrated *in vacuo*. The resulting oil was re suspended in  $\text{Et}_2\text{O}$  and washed twice with 0.1 N  $\text{H}_2\text{SO}_4$ , twice with saturated  $\text{NaHCO}_3$ , and once with brine. The organic layer was then dried over  $\text{MgSO}_4$ , filtered and concentrated *in vacuo*. The residue was then purified on silica gel using 5% methanol in DCM as eluent to provide pure methyl ester.

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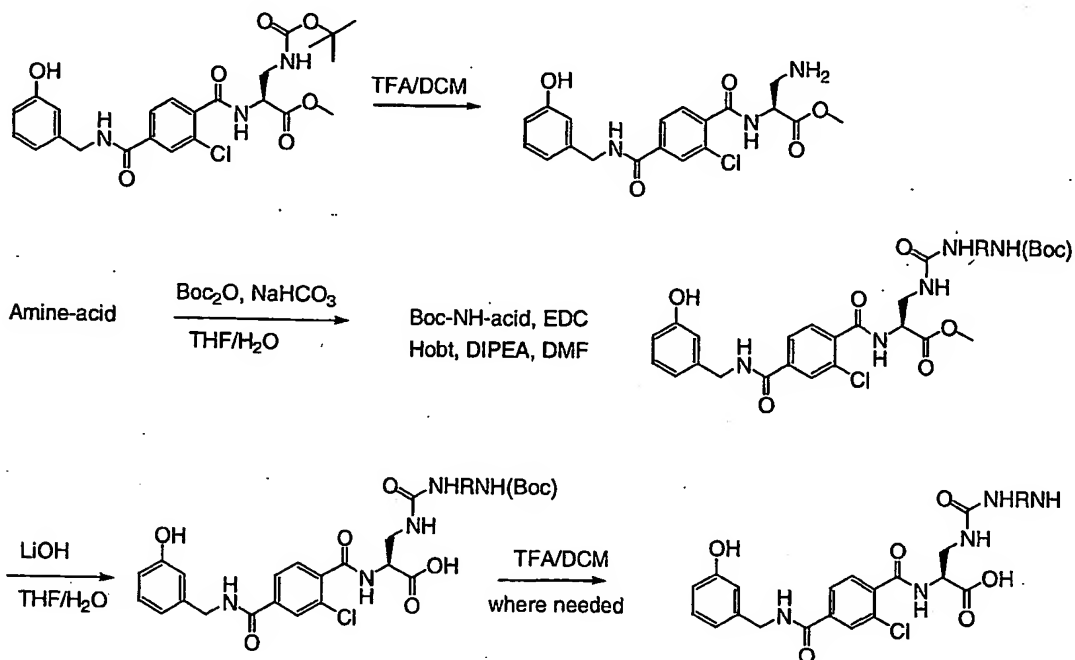
1 equivalent of the resultant methyl ester was dissolved in THF/H<sub>2</sub>O (3/1) and 3 equivalents of LiOH·H<sub>2</sub>O was added. The reaction was monitored by TLC (9/1 DCM/MeOH). Upon completion, the mixture was acidified to pH 2 with 1M HCl and then concentrated *in vacuo*. The resulting solid was re suspended in Et<sub>2</sub>O and washed twice with 0.1 M HCl and once with brine. The organic layer was then dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo*. The Boc, silyl residue was dissolved in a solution of TFA in DCM (1:1) with 3 equivalents of TBAF. After 20 minutes, the reaction was concentrated *in vacuo*. The resulting oil was dissolved in toluene and then reconcentrated *in vacuo*. The resulting acid was then purified by reverse phase HPLC, verified by electrospray mass spectrometry and lyophilized to a powder.

25

# EXAMPLE 5      Synthesis of compounds 26-28, 31



5



10 1 equivalent of dimethyl 2-chloroterephthalic acid was dissolved in DCM and cooled to  $-5^\circ\text{C}$  in an ice/acetone bath under nitrogen. 1 equivalent of  $\text{BBr}_3$  was added drop wise as a solution in DCM over 30 minutes. The reaction was warmed to room temperature and stirred until complete by TLC (DCM/2% HOAc/2% MeOH). The solution was poured onto ice, and the ice was allowed to melt. The mixture was then partitioned with EtOAc and concentrated in vacuo. This product was dissolved in  $\text{H}_2\text{O}$  with the addition of saturated  $\text{NaHCO}_3$  until the pH remained above 8. This solution was partitioned one time with an equal volume of DCM to remove unreacted diester. The basic solution was acidified at  $0^\circ\text{C}$  with concentrated HCl to pH = 1-1.5, and precipitate was extracted twice with equal volumes of EtOAc. The organics were partitioned once with brine and dried over  $\text{MgSO}_4$ , filtered and concentrated in vacuo. Product was 7:1 of the correct regioisomer by HPLC.

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5 The monoester was dissolved in DCM and transferred to a pre-weighed Parr flask containing a stirring bar. The flask was cooled to  $-5^{\circ}\text{C}$  with a dry ice/alcohol bath under nitrogen. Once cool,  $\sim 30$  equivalents of isobutylene was pumped into solution with stirring. 2.1 equivalents  
10 of concentrated sulfuric acid was added and the flask was sealed with a wired rubber stopper and allowed to warm to room temperature with stirring. The solution was stirred until clarification (1-2 days). Once the solution was clear, it was cooled to  $0^{\circ}\text{C}$  in an ice bath. The stopper  
15 was removed and the excess isobutylene was blown off with nitrogen bubbling. Saturated  $\text{NaHCO}_3$  was added to neutralize the acid and the mixture was concentrated in vacuo until no DCM remained. The solution was then partitioned into EtOAc. The organics were partitioned  
20 twice with dilute HCl, twice with saturated  $\text{NaHCO}_3$ , once with brine, dried over  $\text{MgSO}_4$ , filtered and concentrated in vacuo. The resulting product was used with no further purification.

25 1 equivalent of the methyl ester was dissolved in THF/ $\text{H}_2\text{O}$  (3/1) and 3 equivalents of  $\text{LiOH}\cdot\text{H}_2\text{O}$  was added. The reaction was monitored by TLC (9/1 DCM/MeOH). Upon completion, the mixture was acidified carefully to pH 2 with concentrated HCl and then concentrated in vacuo to  
30 remove the THF. The resulting aqueous layer was washed twice with  $\text{Et}_2\text{O}$  and the combined organic layers were washed once with brine. The organic layer was then dried over  $\text{MgSO}_4$ , filtered and concentrated in vacuo. The benzoic acid t-butyl ester was used without further  
35 purification.

1 equivalent of 3-methoxybenzonitrile was placed in a Parr bottle with EtOH, 0.02 equivalents of HCl and 10%

5 (w/w) of 10% Pd on carbon. The vessel was placed in the Parr shaker, charged with 50psi H<sub>2</sub>, and shaken for 12 hours. The reaction filtered through a pad of celite and diluted 1:10 with Et<sub>2</sub>O. Upon standing over night, fine  
10 white needles form. The product was filtered, washed with Et<sub>2</sub>O and dried *in vacuo*. The resulting amine hydrochloride salt was then used with out further purification.

3 equivalents of the benzoic acid t-butyl ester was coupled to 1 equivalent of the amine hydrochloride salt  
15 using 3 equivalents EDC, 1 equivalent of Hobt and 3 equivalents of DIPEA in DMA. The reaction was monitored by TLC (9/1 DCM/MeOH). Upon completion, the mixture was concentrated *in vacuo*. The resulting oil was re suspended in Et<sub>2</sub>O and washed twice with 0.1 N H<sub>2</sub>SO<sub>4</sub>, twice with  
20 saturated NaHCO<sub>3</sub>, and once with brine. The organic layer was then dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo*. The product was then purified on silica get using 5% methanol in DCM as eluent to provide pure t-butyl ester.

25 The t-butyl ester was dissolved in a solution of TFA in DCM (1:1). After 20 minutes, the reaction was concentrated *in vacuo*. The resulting oil was dissolved in toluene and then concentrated *in vacuo* twice.

30 The resulting compound was dissolved in DCM and cooled to -5°C in an ice/acetone bath under nitrogen. 2 equivalents of BBr<sub>3</sub> were added drop wise as a solution in DCM over 30 minutes. The reaction was warmed to room temperature and stirred until complete by TLC (DCM/2% HOAc/2% MeOH). The  
35 solution was poured onto ice, and the ice was allowed to melt. The mixture was then partitioned twice with EtOAc and the combined organic layers were dried over MgSO<sub>4</sub>. The



5 filtrate was then passed over a plug of silica gel and concentrated *in vacuo* to afford pure benzoic acid.

1 equivalent of the benzoic acid, 2 equivalents of commercially available  $\beta$ -Boc-diaminopropionic acid methyl ester, 2 equivalents of EDC, 1 equivalent of HOBt and 3 equivalents of DIPEA were dissolved in DMA. The reaction was stirred at room temperature and monitored by TLC (9/1 DCM/MeOH). Upon completion, the mixture was concentrated *in vacuo*. The resulting oil was re-suspended in Et<sub>2</sub>O and washed twice with 0.1 N H<sub>2</sub>SO<sub>4</sub>, twice with saturated NaHCO<sub>3</sub>, and once with brine. The organic layer was then dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo*. The residue was then purified on silica gel using 5% methanol in DCM as eluent to provide pure methyl ester.

The Boc protected amine was dissolved in a solution of TFA in DCM (1:1). After 20 minutes, the reaction was concentrated *in vacuo*. The resulting oil was dissolved in toluene and then re-concentrated *in vacuo*. 1 equivalent of this amine, 2 equivalents of the appropriate commercially available carboxylic acid ((N-Boc acids were purchased where available. Other acids were purchased as the free amine and Boc protected by the following procedure: The amine was dissolved in a 3:2 THF/H<sub>2</sub>O solution. 1.1 equivalents of solid NaHCO<sub>3</sub> and 1.1 equivalents of Boc<sub>2</sub>O were added and the mixture was stirred overnight. The reaction was concentrated to remove the THF, and the resulting aqueous layer was partitioned with hexanes. The aqueous layer was then acidified to pH 2 with 1N HCl and then partitioned twice with EtOAc. The combined organic layers were dried over MgSO<sub>4</sub> and concentrated *in vacuo*. The resulting product was

5        used without further purification) example 26,  
cyclohexanecarboxylic acid; example 27, isonipecotic  
acid; example 28, D,L-pipecolinic acid; example 31,  
nipecotic acid; 2 equivalents of EDC, 1 equivalent of  
Hobt and 3 equivalents of DIPEA were dissolved DMA. The  
10       reaction was stirred at room temperature and monitored by  
TLC (9/1 DCM/MeOH). Upon completion, the mixture was  
concentrated *in vacuo*. The resulting oil was re suspended  
in Et<sub>2</sub>O and washed twice with 0.1 N H<sub>2</sub>SO<sub>4</sub>, twice with  
saturated NaHCO<sub>3</sub>, and once with brine. The organic layer  
15       was then dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo*. The residue was then purified on silica gel using  
5% methanol in DCM as eluent to provide pure methyl  
ester.

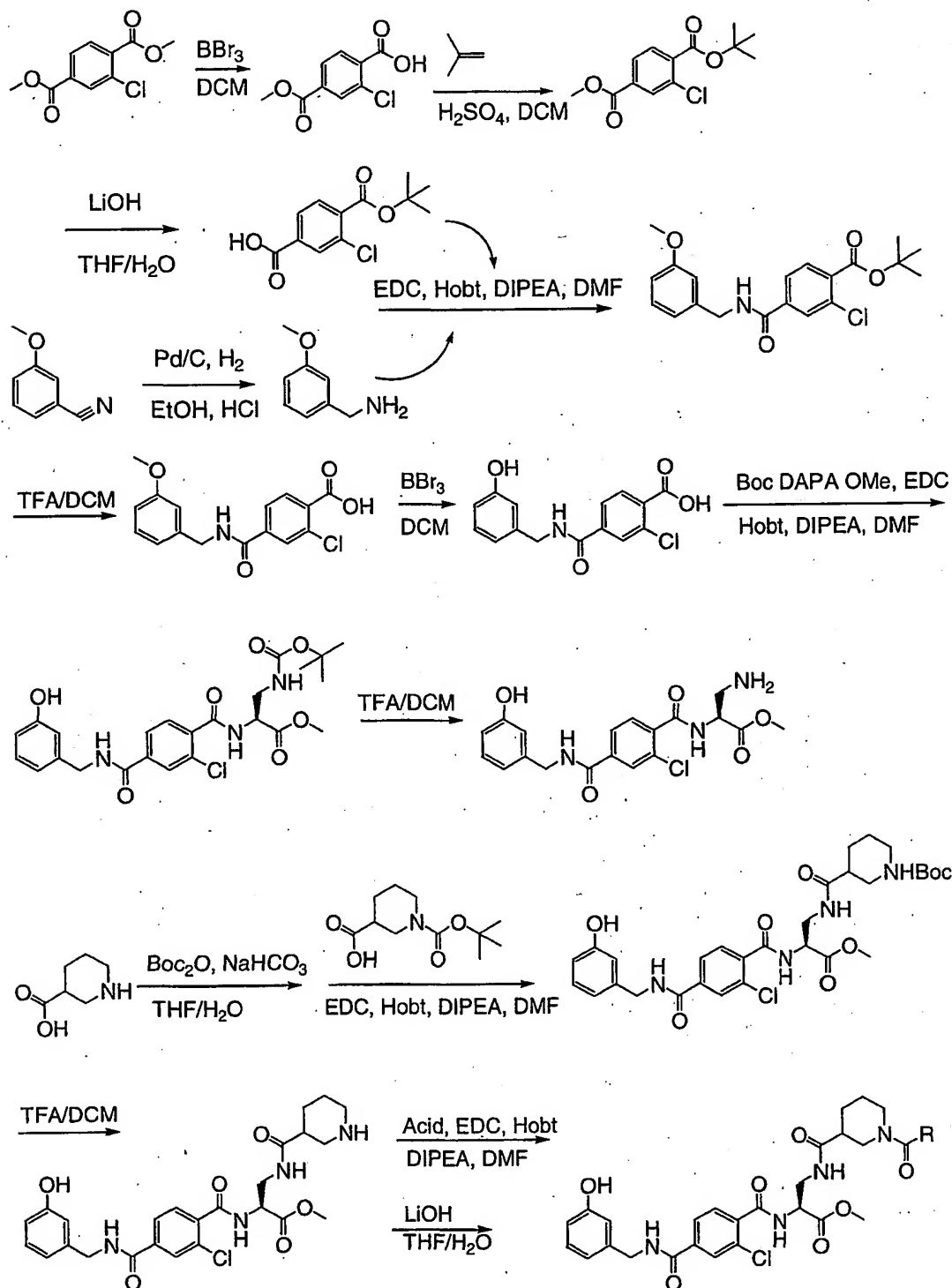
20       1 equivalent of the resultant methyl ester was dissolved  
in THF/H<sub>2</sub>O (3/1) and 3 equivalents of LiOH·H<sub>2</sub>O was added.  
The reaction was monitored by TLC (9/1 DCM/MeOH). Upon  
completion, the mixture was acidified to pH 2 with 1M HCl  
and then concentrated *in vacuo*. The resulting solid was  
25       re suspended in Et<sub>2</sub>O and washed twice with 0.1 M HCl and  
once with brine. The organic layer was then dried over  
MgSO<sub>4</sub>, filtered and concentrated *in vacuo*.

Where appropriate the Boc protected residue was dissolved  
30       in a solution of TFA in DCM (1:1). After 20 minutes, the  
reaction was concentrated *in vacuo*. The resulting oil was  
dissolved in toluene and then re concentrated *in vacuo*.  
The resulting acid was then purified by reverse phase  
HPLC, verified by electrospray mass spectrometry and  
35       lyophilized to a powder.

5

## EXAMPLE 6

## Synthesis of compounds 29, 30



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1 equivalent of dimethyl 2-chloroterephthalic acid was dissolved in DCM and cooled to  $-5^\circ\text{C}$  in an ice/acetone bath under nitrogen. 1 equivalent of  $\text{BBr}_3$  was added drop

5 wise as a solution in DCM over 30 minutes. The reaction  
was warmed to room temperature and stirred until complete  
by TLC (DCM/2% HOAc/2% MeOH). The solution was poured  
onto ice, and the ice was allowed to melt. The mixture  
was then partitioned with EtOAc and concentrated in  
10 vacuo. This product was dissolved in H<sub>2</sub>O with the addition  
of saturated NaHCO<sub>3</sub> until the pH remained above 8. This  
solution was partitioned one time with an equal volume  
of DCM to remove unreacted diester. The basic solution  
was acidified at 0°C. with concentrated HCl to pH = 1-  
15 1.5, and precipitate was extracted twice with equal  
volumes of EtOAc. The organics were partitioned once  
with brine and dried over MgSO<sub>4</sub>, filtered and concentrated  
in vacuo. Product was 7:1 of the correct regioisomer by  
HPLC.

20 The monoester was dissolved in DCM and transferred to a  
pre-weighed Parr flask containing a stirring bar. The  
flask was cooled to -5°C with a dry ice/alcohol bath  
under nitrogen. Once cool, ~30 equivalents of isobutylene  
25 was pumped into solution with stirring. 2.1 equivalents  
of concentrated sulfuric acid was added and the flask was  
sealed with a wired rubber stopper and allowed to warm to  
room temperature with stirring. The solution was stirred  
until clarification (1-2 days). Once the solution was  
30 clear, it was cooled to 0°C in an ice bath. The stopper  
was removed and the excess isobutylene was blown off with  
nitrogen bubbling. Saturated NaHCO<sub>3</sub> was added to  
neutralize the acid and the mixture was concentrated in  
vacuo until no DCM remained. The solution was then  
35 partitioned into EtOAc. The organics were partitioned  
twice with dilute HCl, twice with saturated NaHCO<sub>3</sub>, once  
with brine, dried over MgSO<sub>4</sub>, filtered and concentrated in

5       *vacuo*. The resulting product was used with no further purification.

10       1 equivalent of the methyl ester was dissolved in THF/H<sub>2</sub>O (3/1) and 3 equivalents of LiOH·H<sub>2</sub>O were added. The reaction was monitored by TLC (9/1 DCM/MeOH). Upon completion, the mixture was acidified carefully to pH 2 with concentrated HCl and then concentrated in *vacuo* to remove the THF. The resulting aqueous layer was washed twice with Et<sub>2</sub>O and the combined organic layers were  
15       washed once with brine. The organic layer was then dried over MgSO<sub>4</sub>, filtered and concentrated in *vacuo*. The benzoic acid t-butyl ester was used without further purification.

20       1 equivalent of 3-methoxybenzonitrile was placed in a Parr bottle with EtOH, 0.02 equivalents of HCl and 10% (w/w) of 10% Pd on carbon. The vessel was placed in the Parr shaker, charged with 50psi H<sub>2</sub>, and shaken for 12 hours. The reaction filtered through a pad of celite and  
25       diluted 1:10 with Et<sub>2</sub>O. Upon standing over night, fine white needles form. The product was filtered, washed with Et<sub>2</sub>O and dried in *vacuo*. The resulting amine hydrochloride salt was then used with out further purification.

30       3 equivalents of the benzoic acid t-butyl ester was coupled to 1 equivalent of the amine hydrochloride salt using 3 equivalents EDC, 1 equivalent of Hobt and 3 equivalents of DIPEA in DMA. The reaction was monitored by TLC (9/1 DCM/MeOH). Upon completion, the mixture was  
35       concentrated in *vacuo*. The resulting oil was re suspended in Et<sub>2</sub>O and washed twice with 0.1 N H<sub>2</sub>SO<sub>4</sub>, twice with saturated NaHCO<sub>3</sub>, and once with brine. The organic layer was then dried over MgSO<sub>4</sub>, filtered and concentrated in

5        *vacuo*. The product was then purified on silica gel using 5% methanol in DCM as eluent to provide pure t-butyl ester.

10        The t-butyl ester was dissolved in a solution of TFA in DCM (1:1). After 20 minutes, the reaction was concentrated in *vacuo*. The resulting oil was dissolved in toluene and then concentrated in *vacuo* twice.

15        The resulting compound was dissolved in DCM and cooled to -5°C in an ice/acetone bath under nitrogen. 2 equivalents of BBr<sub>3</sub> were added drop wise as a solution in DCM over 30 minutes. The reaction was warmed to room temperature and stirred until complete by TLC (DCM/2% HOAc/2% MeOH). The solution was poured onto ice, and the ice was allowed to melt. The mixture was then partitioned twice with EtOAc and the combined organic layers were dried over MgSO<sub>4</sub>. The filtrate was then passed over a plug of silica gel and concentrated in *vacuo* to afford pure benzoic acid.

25        1 equivalent of the benzoic acid, 2 equivalents of commercially available  $\alpha$ -Boc-diaminopropionic acid methyl ester, 2 equivalents of EDC, 1 equivalent of HOBt and 3 equivalents of DIPEA were dissolved in DMA. The reaction was stirred at room temperature and monitored by TLC (9/1 DCM/MeOH). Upon completion, the mixture was concentrated in *vacuo*. The resulting oil was re suspended in Et<sub>2</sub>O and washed twice with 0.1 N H<sub>2</sub>SO<sub>4</sub>, twice with saturated NaHCO<sub>3</sub>, and once with brine. The organic layer was then dried over MgSO<sub>4</sub>, filtered and concentrated in *vacuo*. The residue was then purified on silica gel using 5% methanol in DCM as eluent to provide pure Boc methyl ester.

5 1 equivalent of commercially available nipecotic acid was dissolved in a 3:2 THF/H<sub>2</sub>O solution. 1.1 equivalents of solid NaHCO<sub>3</sub> and 1.1 equivalents of Boc<sub>2</sub>O were added and the mixture was stirred overnight. The reaction was concentrated to remove the THF, and the resulting aqueous  
10 layer was partitioned with hexanes. The aqueous layer was then acidified to pH 2 with 1N HCl and then partitioned twice with EtOAc. The combined organic layers were dried over MgSO<sub>4</sub> and concentrated *in vacuo*. The resulting Boc protected nipecotic acid was used without further  
15 purification.

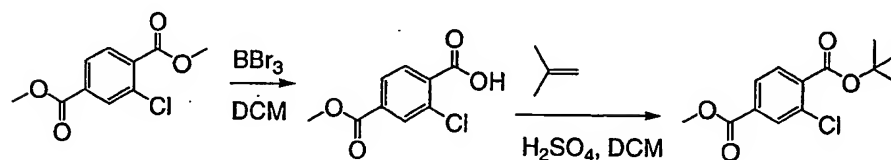
The Boc methyl ester was dissolved in a solution of TFA in DCM (1:1). After 20 minutes, the reaction was concentrated *in vacuo*. The resulting oil was dissolved in  
20 toluene and then re concentrated *in vacuo*. 1 equivalent of this amine, 2 equivalents of resulting Boc protected nipecotic acid, 2 equivalents of EDC, 1 equivalent of Hobt and 3 equivalents of DIPEA were dissolved DMA. The reaction was stirred at room temperature and monitored by  
25 TLC (9/1 DCM/MeOH). Upon completion, the mixture was concentrated *in vacuo*. The resulting oil was re suspended in Et<sub>2</sub>O and washed twice with 0.1 N H<sub>2</sub>SO<sub>4</sub>, twice with saturated NaHCO<sub>3</sub>, and once with brine. The organic layer was then dried over MgSO<sub>4</sub>, filtered and concentrated in  
30 *vacuo*. The residue was then purified on silica gel using 5% methanol in DCM as eluent to provide pure product.

This Boc protected product was dissolved in a solution of TFA in DCM (1:1). After 20 minutes, the reaction was  
35 concentrated *in vacuo*. The resulting oil was dissolved in toluene and then concentrated *in vacuo* twice to provide pure amine. 1 equivalent of this amine, 2 equivalents of the appropriate commercially available acid (example 29;

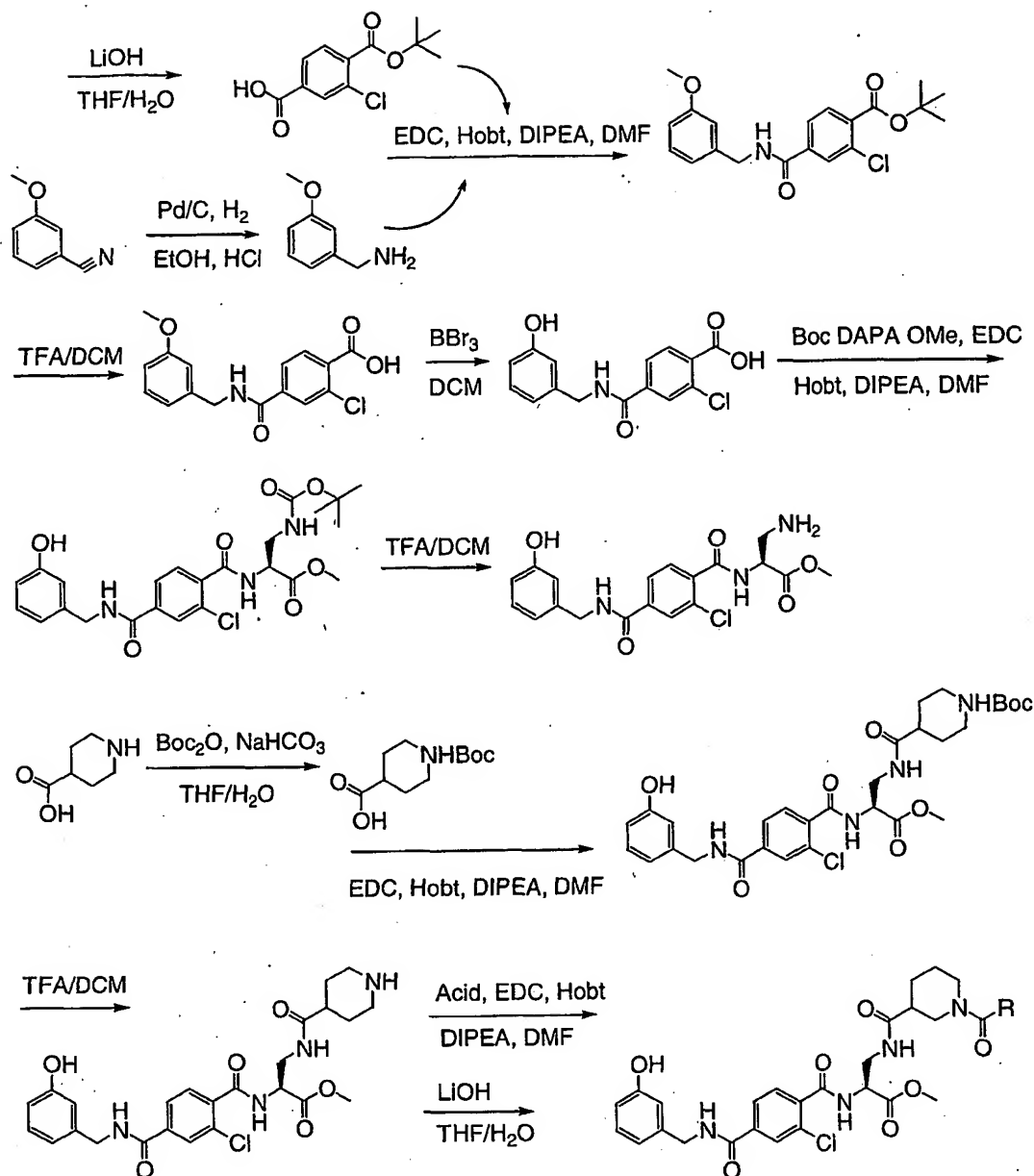
5 propionic acid; example 30, acetic acid), 2 equivalents  
of EDC, 1 equivalent of Hobt and 3 equivalents of DIPEA  
were dissolved DMA. The reaction was stirred at room  
temperature and monitored by TLC (9/1 DCM/MeOH). Upon  
completion, the mixture was concentrated *in vacuo*. The  
10 resulting oil was re suspended in Et<sub>2</sub>O and washed twice  
with 0.1 N H<sub>2</sub>SO<sub>4</sub>, twice with saturated NaHCO<sub>3</sub>, and once  
with brine. The organic layer was then dried over MgSO<sub>4</sub>,  
filtered and concentrated *in vacuo*. The residue was then  
purified on silica gel using 5% methanol in DCM as eluent  
15 to provide pure product.

1 equivalent of the resultant methyl ester was dissolved  
in THF/H<sub>2</sub>O (3/1) and 3 equivalents of LiOH·H<sub>2</sub>O was added.  
The reaction was monitored by TLC (9/1 DCM/MeOH). Upon  
20 completion, the mixture was acidified to pH 2 with 1M HCl  
and then concentrated *in vacuo*. The resulting solid was  
re suspended in Et<sub>2</sub>O and washed twice with 0.1 M HCl and  
once with brine. The organic layer was then dried over  
MgSO<sub>4</sub>, filtered and concentrated *in vacuo*. The resulting  
25 acid was then purified by reverse phase HPLC, verified by  
electrospray mass spectrometry and lyophilized to a  
powder.

30 EXAMPLE 7 Synthesis of compounds 32-34







10

1 equivalent of dimethyl 2- chloroterephthalic acid was dissolved in DCM and cooled to  $-5^{\circ}\text{C}$  in an ice/acetone bath under nitrogen. 1 equivalent of  $\text{BBr}_3$  was added drop wise as a solution in DCM over 30 minutes. The reaction was warmed to room temperature and stirred until complete by TLC (DCM/2% HOAc/2% MeOH). The solution was poured onto ice, and the ice was allowed to melt. The mixture was then partitioned with EtOAc and concentrated in vacuo. This product was dissolved in  $\text{H}_2\text{O}$  with the addition

- 5 of saturated  $\text{NaHCO}_3$  until the pH remained above 8. This solution was partitioned one time with an equal volume of DCM to remove unreacted diester. The basic solution was acidified at  $0^\circ\text{C}$  with concentrated  $\text{HCl}$  to  $\text{pH} = 1-1.5$ , and precipitate was extracted twice with equal  
10 volumes of  $\text{EtOAc}$ . The organics were partitioned once with brine and dried over  $\text{MgSO}_4$ , filtered and concentrated *in vacuo*. Product was 7:1 of the correct regioisomer by HPLC.
- 15 The monoester was dissolved in DCM and transferred to a pre-weighed Parr flask containing a stirring bar. The flask was cooled to  $-5^\circ\text{C}$  with a dry ice/alcohol bath under nitrogen. Once cool, ~30 equivalents of isobutylene was pumped into solution with stirring. 2.1 equivalents  
20 of concentrated sulfuric acid was added and the flask was sealed with a wired rubber stopper and allowed to warm to room temperature with stirring. The solution was stirred until clarification (1-2 days). Once the solution was clear, it was cooled to  $0^\circ\text{C}$  in an ice bath. The stopper  
25 was removed and the excess isobutylene was blown off with nitrogen bubbling. Saturated  $\text{NaHCO}_3$  was added to neutralize the acid and the mixture was concentrated *in vacuo* until no DCM remained. The solution was then partitioned into  $\text{EtOAc}$ . The organics were partitioned  
30 twice with dilute  $\text{HCl}$ , twice with saturated  $\text{NaHCO}_3$ , once with brine, dried over  $\text{MgSO}_4$ , filtered and concentrated *in vacuo*. The resulting product was used with no further purification.
- 35 1 equivalent of the methyl ester was dissolved in  $\text{THF}/\text{H}_2\text{O}$  (3/1) and 3 equivalents of  $\text{LiOH}\cdot\text{H}_2\text{O}$  was added. The reaction was monitored by TLC (9/1  $\text{DCM}/\text{MeOH}$ ). Upon completion, the mixture was acidified carefully to  $\text{pH} 2$

5 with concentrated HCl and then concentrated in vacuo to  
remove the THF. The resulting aqueous layer was washed  
twice with Et<sub>2</sub>O and the combined organic layers were  
washed once with brine. The organic layer was then dried  
over MgSO<sub>4</sub>, filtered and concentrated in vacuo. The  
10 benzoic acid t-butyl ester was used without further  
purification.

1 equivalent of 3-methoxybenzonitrile was placed in a  
Parr bottle with EtOH, 0.02 equivalents of HCl and 10%  
15 (w/w) of 10% Pd on carbon. The vessel was placed in the  
Parr shaker, charged with 50psi H<sub>2</sub>, and shaken for 12  
hours. The reaction filtered through a pad of celite and  
diluted 1:10 with Et<sub>2</sub>O. Upon standing over night, fine  
white needles form. The product was filtered, washed with  
20 Et<sub>2</sub>O and dried in vacuo. The resulting amine hydrochloride  
salt was then used with out further purification.

3 equivalents of the benzoic acid t-butyl ester was  
coupled to 1 equivalent of the amine hydrochloride salt  
25 using 3 equivalents EDC, 1 equivalent of Hobt and 3  
equivalents of DIPEA in DMA. The reaction was monitored  
by TLC (9/1 DCM/MeOH). Upon completion, the mixture was  
concentrated in vacuo. The resulting oil was re suspended  
in Et<sub>2</sub>O and washed twice with 0.1 N H<sub>2</sub>SO<sub>4</sub>, twice with  
30 saturated NaHCO<sub>3</sub>, and once with brine. The organic layer  
was then dried over MgSO<sub>4</sub>, filtered and concentrated in  
vacuo. The product was then purified on silica get using  
5% methanol in DCM as eluent to provide pure t-butyl  
ester.

35

The t-butyl ester was dissolved in a solution of TFA in  
DCM (1:1). After 20 minutes, the reaction was

5 concentrated in *vacuo*. The resulting oil was dissolved in toluene and then concentrated in *vacuo* twice.

The resulting compound was dissolved in DCM and cooled to -5°C in an ice/acetone bath under nitrogen. 2 equivalents  
10 of BBr<sub>3</sub> were added drop wise as a solution in DCM over 30 minutes. The reaction was warmed to room temperature and stirred until complete by TLC (DCM/2% HOAc/2% MeOH). The solution was poured onto ice, and the ice was allowed to melt. The mixture was then partitioned twice with EtOAc  
15 and the combined organic layers were dried over MgSO<sub>4</sub>. The filtrate was then passed over a plug of silica gel and concentrated in *vacuo* to afford pure benzoic acid.

1 equivalent of the benzoic acid, 2 equivalents of  
20 commercially available  $\alpha$ -Boc-diaminopropionic acid methyl ester, 2 equivalents of EDC, 1 equivalent of Hobt and 3 equivalents of DIPEA were dissolved DMA. The reaction was stirred at room temperature and monitored by TLC (9/1 DCM/MeOH). Upon completion, the mixture was  
25 concentrated in *vacuo*. The resulting oil was re suspended in Et<sub>2</sub>O and washed twice with 0.1 N H<sub>2</sub>SO<sub>4</sub>, twice with saturated NaHCO<sub>3</sub>, and once with brine. The organic layer was then dried over MgSO<sub>4</sub>, filtered and concentrated in *vacuo*. The residue was then purified on silica gel using  
30 5% methanol in DCM as eluent to provide pure Boc methyl ester.

1 equivalent of commercially available isonipecotic acid was dissolved in a 3:2 THF/H<sub>2</sub>O solution. 1.1 equivalents  
35 of solid NaHCO<sub>3</sub> and 1.1 equivalents of Boc<sub>2</sub>O were added and the mixture was stirred overnight. The reaction was concentrated to remove the THF, and the resulting aqueous layer was partitioned with hexanes. The aqueous layer was

5 then acidified to pH 2 with 1N HCl and then partitioned twice with EtOAc. The combined organic layers were dried over  $\text{MgSO}_4$  and concentrated in vacuo. The resulting Boc protected isonipecotic acid was used without further purification.

10

The Boc methyl ester was dissolved in a solution of TFA in DCM (1:1). After 20 minutes, the reaction was concentrated in vacuo. The resulting oil was dissolved in toluene and then re concentrated in vacuo. 1 equivalent of this amine, 2 equivalents of resulting Boc protected isonipecotic acid, 2 equivalents of EDC, 1 equivalent of Hobt and 3 equivalents of DIPEA were dissolved DMA. The reaction was stirred at room temperature and monitored by TLC (9/1 DCM/MeOH). Upon completion, the mixture was concentrated in vacuo. The resulting oil was re suspended in  $\text{Et}_2\text{O}$  and washed twice with 0.1 N  $\text{H}_2\text{SO}_4$ , twice with saturated  $\text{NaHCO}_3$ , and once with brine. The organic layer was then dried over  $\text{MgSO}_4$ , filtered and concentrated in vacuo. The residue was then purified on silica gel using 25 5% methanol in DCM as eluent to provide pure product.

This Boc protected product was dissolved in a solution of TFA in DCM (1:1). After 20 minutes, the reaction was concentrated in vacuo. The resulting oil was dissolved in toluene and then concentrated in vacuo twice to provide pure amine. 1 equivalent of this amine, 2 equivalents of the appropriate commercially available acid (example 32; propionic acid; example 33, butyric acid; example 34, acetic acid), 2 equivalents of EDC, 1 equivalent of Hobt and 3 equivalents of DIPEA were dissolved DMA. The reaction was stirred at room temperature and monitored by TLC (9/1 DCM/MeOH). Upon completion, the mixture was concentrated in vacuo. The resulting oil was re suspended

5 in Et<sub>2</sub>O and washed twice with 0.1 N H<sub>2</sub>SO<sub>4</sub>, twice with saturated NaHCO<sub>3</sub>, and once with brine. The organic layer was then dried over MgSO<sub>4</sub>, filtered and concentrated in vacuo. The residue was then purified on silica gel using 5% methanol in DCM as eluent to provide pure product.

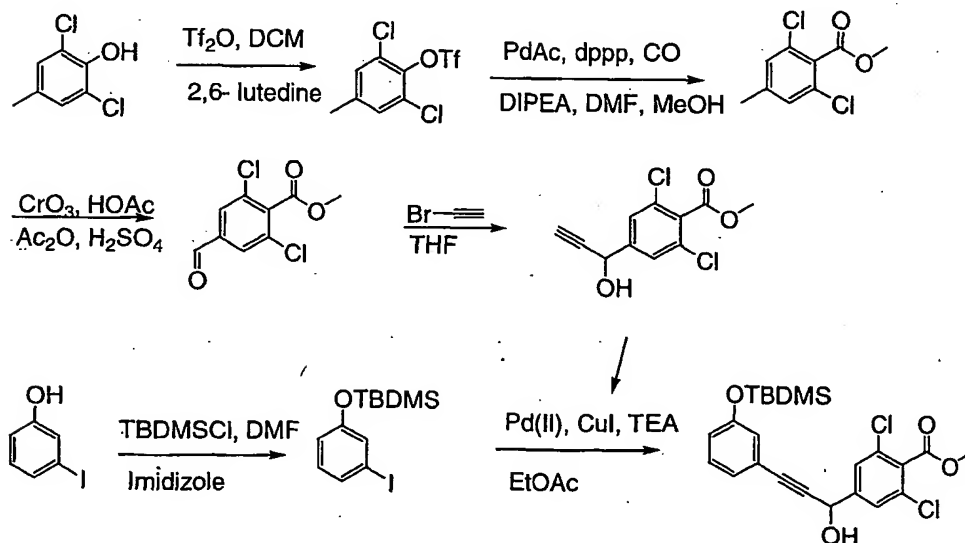
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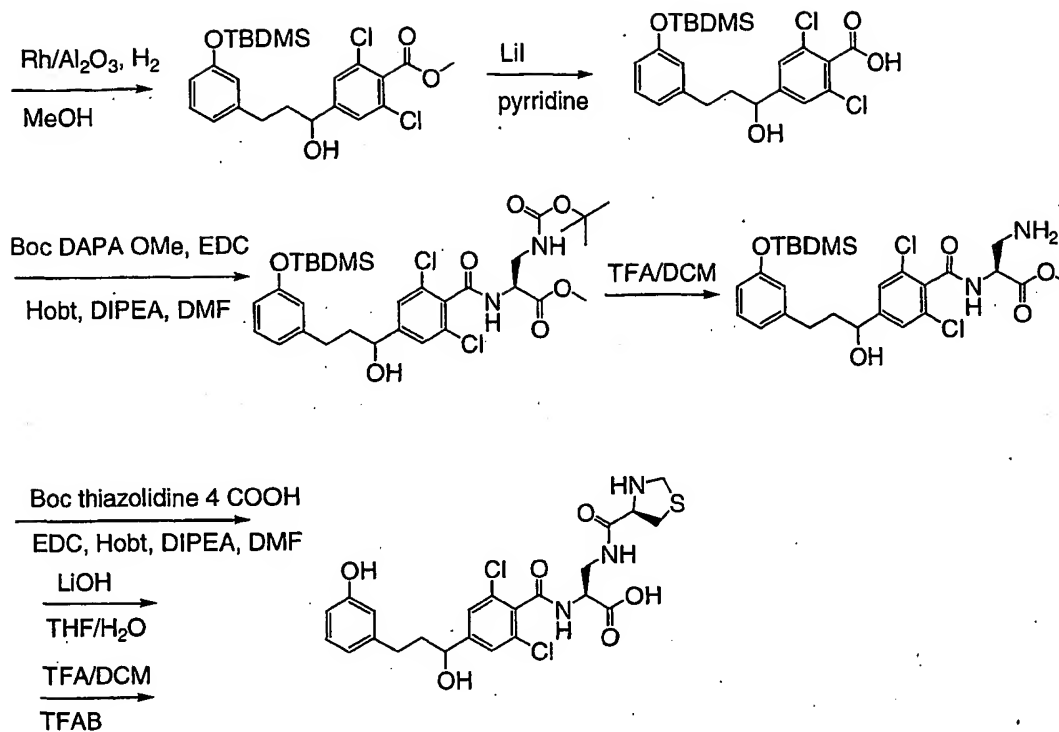
1 equivalent of the resultant methyl ester was dissolved in THF/H<sub>2</sub>O (3/1) and 3 equivalents of LiOH·H<sub>2</sub>O were added. The reaction was monitored by TLC (9/1 DCM/MeOH). Upon completion, the mixture was acidified to pH 2 with 1M HCl and then concentrated in vacuo. The resulting solid was re suspended in Et<sub>2</sub>O and washed twice with 0.1 M HCl and once with brine. The organic layer was then dried over MgSO<sub>4</sub>, filtered and concentrated in vacuo. The resulting acid was then purified by reverse phase HPLC, verified by electrospray mass spectrometry and lyophilized to a powder.

20

EXAMPLE 8 Synthesis of compounds 36

25





1 equivalent of 2, 6-Dichloro-4-methyl phenol was dissolved in DCM containing 2.6 equivalents of 2, 6-lutidine and the mixture was cooled to  $-78^{\circ}\text{C}$ . After adding 1.25 equivalents of triflic anhydride the stirring reaction was allowed to warm to room temperature overnight. The reaction was then concentrated, and the residue was partitioned between  $\text{Et}_2\text{O}$  and  $\text{H}_2\text{O}$ . The aqueous layer was extracted with  $\text{Et}_2\text{O}$  and the combined organic layers were dried over  $\text{MgSO}_4$  and concentrated *in vacuo*. The residue was purified by silica gel flash chromatography (9:1 hexane/ $\text{Et}_2\text{O}$ ) to provide the pure triflate.

To a stirring solution of 1 equivalent of the triflate in a 2/1 mixture of DMF/MeOH was added 0.15 equivalents of 1, 3-bis(diphenylphosphino)-propane and 2.5 equivalents of TEA. Carbon monoxide gas was bubbled through this solution for 15 minutes, then 0.15 equivalents of  $\text{Pd}(\text{OAc})_2$  was added and the reaction was stirred at  $70^{\circ}\text{C}$

5 for 5-7 hours under an atmosphere of CO (using a balloon  
filled with CO). The reaction was then concentrated in  
vacuo, and the residue was partitioned between Et<sub>2</sub>O and  
H<sub>2</sub>O. The aqueous layer was extracted twice with Et<sub>2</sub>O and  
the combined organic layers were dried over MgSO<sub>4</sub>,  
10 filtered through a plug of silica gel and concentrated in  
vacuo. The residue was purified by silica gel flash  
chromatography (9:1:0.02 hexane/DCM/Et<sub>2</sub>O) to provide the  
pure tolyl methyl ester.

15 1 equivalent of the tolyl methyl ester was dissolved in  
acetic anhydride and HOAc, then cooled in an ice-salt  
bath (-5°C) before concentrated H<sub>2</sub>SO<sub>4</sub> was added. A  
solution of CrO<sub>3</sub> (2.6 equivalents) in acetic anhydride and  
HOAc was added drop wise and the reaction was stirred for  
20 3.5 hours at -5°C. The reaction was poured into ice H<sub>2</sub>O  
and stirred for 30 min. The mixture was extracted three  
times with ethyl ether. The combined organic layers were  
washed with saturated NaHCO<sub>3</sub> and brine, then dried over  
MgSO<sub>4</sub> and concentrated in vacuo to an oil. Toluene was  
25 added to the oil and the solution concentrated in vacuo  
again. This was repeated to obtain a crystalline solid.  
The solid was dissolved in methanol and concentrated HCl  
and heated at reflux for 12 hours. The reaction was  
concentrated in vacuo and the residue was purified by  
30 silica gel flash chromatography (9:1 hexane/Et<sub>2</sub>O) to  
provide the pure aldehyde.

A solution of 1 equivalent of the aldehyde in THF was  
cooled to -78°C and 1.1 equivalents of 0.5M  
35 ethynylmagnesium bromide/THF was added. After stirring  
the reaction at room temperature for 3 hours, it was  
diluted with Et<sub>2</sub>O and washed twice with 10% citric acid.  
The combined aqueous layers were back-extracted once with



5 Et<sub>2</sub>O. The combined organic layers were washed twice with saturated aqueous NaHCO<sub>3</sub>, dried over MgSO<sub>4</sub> and concentrated in vacuo. The residue was purified by silica gel flash chromatography (4:1 to 3:2 hexane/Et<sub>2</sub>O) to provide the pure alkyne.

10

1 equivalent of 3-Iodophenol, 2.2 equivalents of t-butyltrimethylsilyl chloride and 3 equivalents of imidazole were dissolved in DMF and stirred at room temperature. The reaction was monitored by TLC (9/1 DCM/MeOH). Upon reaction completion, the mixture was concentrated in vacuo. The resulting oil was re suspended in Et<sub>2</sub>O and washed twice with saturated NaHCO<sub>3</sub>, and once with brine. The organic layer was then dried over MgSO<sub>4</sub>, filtered and concentrated in vacuo. The product was then used without further purification.

20

1 equivalent of the silyl iodide was dissolved in EtOAc and the solution was degassed by passing N<sub>2</sub> through a pipette and into the solution for 10 minutes. 1.25 equivalents of the alkyne was added, followed by 0.02 equivalents of dichlorobis(triphenylphosphine)-palladium(II), 0.04 equivalents of CuI and 5 equivalents TEA. The reaction was stirred for 14 hours, diluted with EtOAc, washed twice with 5% Na<sub>2</sub>•EDTA, brine and then dried over MgSO<sub>4</sub> and concentrated in vacuo. The residue was purified by silica gel flash chromatography (gradient elution, using Et<sub>2</sub>O to EtOAc) to provide the pure aryl alkyne.

30

1 equivalent of the aryl alkyne was dissolved in MeOH and the solution was degassed by passing N<sub>2</sub> through a pipette and into the solution for 10 minutes. The 5% Rh/Al<sub>2</sub>O<sub>3</sub> was added, one balloon-full of hydrogen was passed through the solution, and the reaction was stirred under an

35

5 atmosphere of  $H_2$  (using a balloon) for 7 hours, after which the reaction was filtered through a pad of celite and concentrated in *vacuo*. The residue was purified by silica gel flash chromatography (gradient elution, using  $Et_2O$  to  $EtOAc$ ) to provide the pure product.

10

2.3 equivalents of lithium iodide was added to 1 equivalent of the methyl ester in pyridine, and the mixture heated at reflux for 8 hours. The reaction was concentrated in *vacuo* and the residue was partitioned between  $EtOAc$  and 1N  $HCl$ . The aqueous layer was extracted 15 three times with  $EtOAc$ , and the combined organic layers were washed with 1M  $NaHCO_3$ , dried over  $MgSO_4$  and concentrated in *vacuo*. The residue was dissolved in NMM and the solution concentrated in *vacuo*. The residue was 20 taken up in DCM and then washed three times with 1N  $HCl$ . The organic layer was dried over  $MgSO_4$  and concentrated in *vacuo* to provide the benzoic acid in high enough purity to be used without further purification.

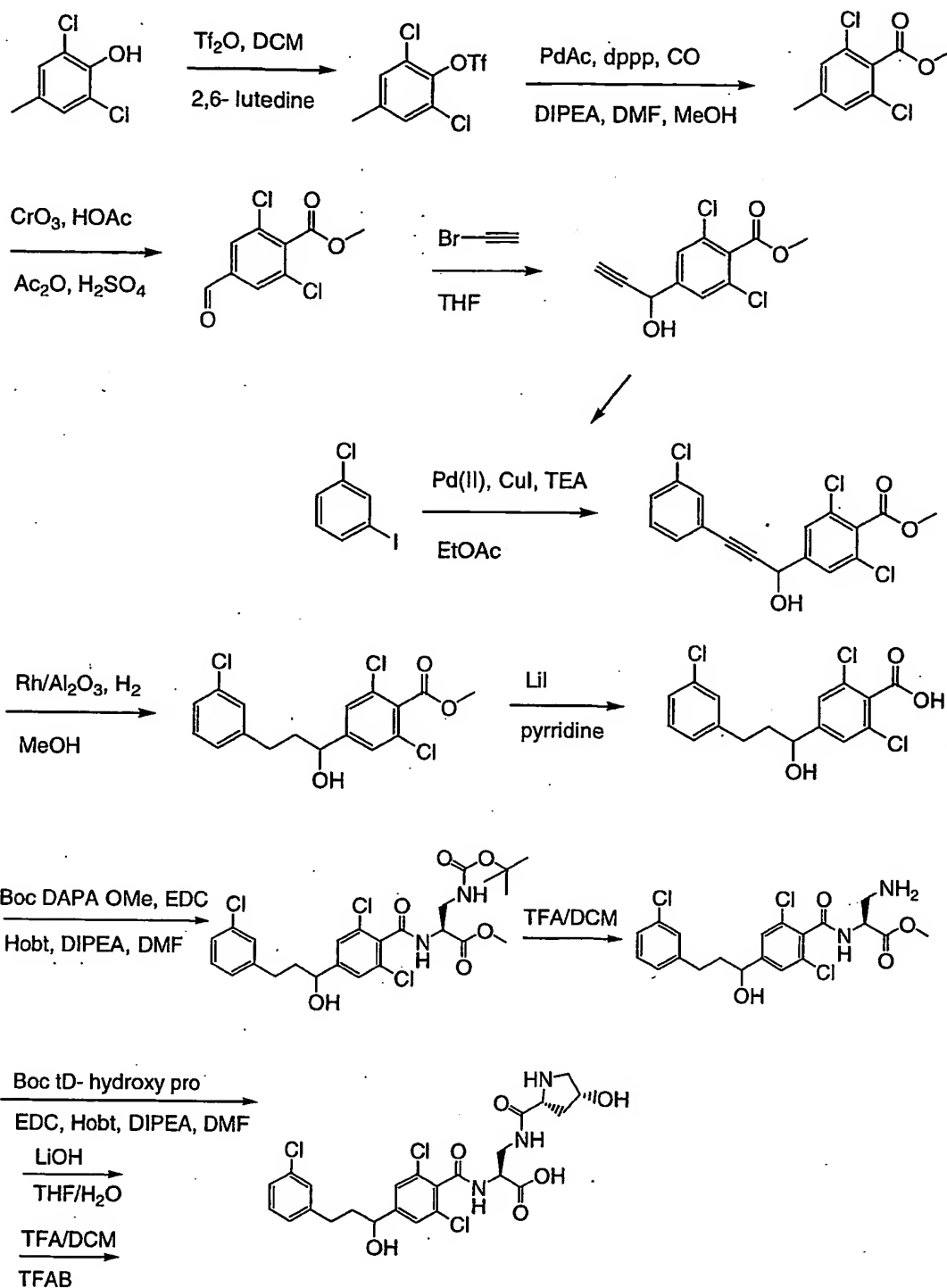
25 1 equivalent of the acid, 2 equivalents of commercially available  $\beta$ -Boc-diaminopropionic acid methyl ester, 2 equivalents of EDC, 1 equivalent of Hobt and 3 equivalents of DIPEA were dissolved DMA. The reaction was stirred at room temperature and monitored by TLC (9/1 30 DCM/MeOH). Upon completion, the mixture was concentrated in *vacuo*. The resulting oil was re suspended in  $Et_2O$  and washed twice with 0.1 N  $H_2SO_4$ , twice with saturated  $NaHCO_3$ , and once with brine. The organic layer was then dried over  $MgSO_4$ , filtered and concentrated in *vacuo*. The 35 residue was then purified on silica gel using 5% methanol in DCM as eluent to provide pure methyl ester.

5       The Boc protected amine was dissolved in a solution of  
TFA in DCM (1:1). After 20 minutes, the reaction was  
concentrated *in vacuo*. The resulting oil was dissolved in  
toluene and then reconcentrated *in vacuo*. 1 equivalent of  
this amine, 2 equivalents of Boc-L-thiazolidine-4-  
10       carboxylic acid, 2 equivalents of EDC, 1 equivalent of  
Hobt and 3 equivalents of DIPEA were dissolved DMA. The  
reaction was stirred at room temperature and monitored by  
TLC (9/1 DCM/MeOH). Upon completion, the mixture was  
concentrated *in vacuo*. The resulting oil was re suspended  
15       in Et<sub>2</sub>O and washed twice with 0.1 N H<sub>2</sub>SO<sub>4</sub>, twice with  
saturated NaHCO<sub>3</sub>, and once with brine. The organic layer  
was then dried over MgSO<sub>4</sub>, filtered and concentrated in  
*vacuo*. The residue was then purified on silica gel using  
5% methanol in DCM as eluent to provide pure methyl  
20       ester.

1 equivalent of the resultant methyl ester was dissolved  
in THF/H<sub>2</sub>O (3/1) and 3 equivalents of LiOH•H<sub>2</sub>O was added.  
The reaction was monitored by TLC (9/1 DCM/MeOH). Upon  
25       completion, the mixture was acidified to pH 2 with 1M HCl  
and then concentrated *in vacuo*. The resulting solid was  
re suspended in Et<sub>2</sub>O and washed twice with 0.1 M HCl and  
once with brine. The organic layer was then dried over  
MgSO<sub>4</sub>, filtered and concentrated *in vacuo*.

30       The Boc, silyl residue was dissolved in a solution of TFA  
in DCM (1:1) with 3 equivalents of TBAF. After 20  
minutes, the reaction was concentrated *in vacuo*. The  
resulting oil was dissolved in toluene and then  
reconcentrated *in vacuo*. The resulting acid was then  
35       purified by reverse phase HPLC, verified by electrospray  
mass spectrometry and lyophilized to a powder.

5      EXAMPLE 9      Synthesis of compounds 37



15 1 equivalent of 2, 6-Dichloro-4-methyl phenol was dissolved in DCM containing 2.6 equivalents of 2, 6-lutidine and the mixture was cooled to -78°C. After

5 adding 1.25 equivalents of triflic anhydride the stirring  
reaction was allowed to warm to room temperature  
overnight. The reaction was then concentrated, and the  
residue was partitioned between Et<sub>2</sub>O and H<sub>2</sub>O. The aqueous  
layer was extracted with Et<sub>2</sub>O and the combined organic  
10 layers were dried over MgSO<sub>4</sub> and concentrated in vacuo.  
The residue was purified by silica gel flash  
chromatography (9:1 hexane/Et<sub>2</sub>O) to provide the pure  
triflate.

15 To a stirring solution of 1 equivalent of the triflate in  
a 2/1 mixture of DMF/MeOH was added 0.15 equivalents of  
1, 3-bis(diphenylphosphino)-propane and 2.5 equivalents  
of TEA. Carbon monoxide gas was bubbled through this  
solution for 15 minutes, then 0.15 equivalents of  
20 Pd(OAc)<sub>2</sub> was added and the reaction was stirred at 70°C  
for 5-7 hours under an atmosphere of CO (using a balloon  
filled with CO). The reaction was then concentrated in  
vacuo, and the residue was partitioned between Et<sub>2</sub>O and  
H<sub>2</sub>O. The aqueous layer was extracted twice with Et<sub>2</sub>O and  
25 the combined organic layers were dried over MgSO<sub>4</sub>,  
filtered through a plug of silica gel and concentrated in  
vacuo. The residue was purified by silica gel flash  
chromatography (9:1:0.02 hexane/DCM/Et<sub>2</sub>O) to provide the  
pure tolyl methyl ester.

30 1 equivalent of the tolyl methyl ester was dissolved in  
acetic anhydride and HOAc, then cooled in an ice-salt  
bath (-5°C) before concentrated H<sub>2</sub>SO<sub>4</sub> was added. A  
solution of CrO<sub>3</sub> (2.6 equivalents) in acetic anhydride and  
35 HOAc was added drop wise and the reaction was stirred for  
3.5 hours at -5°C. The reaction was poured into ice H<sub>2</sub>O  
and stirred for 30 min. The mixture was extracted three  
times with ethyl ether. The combined organic layers were

5 washed with saturated  $\text{NaHCO}_3$  and brine, then dried over  $\text{MgSO}_4$  and concentrated in vacuo to an oil. Toluene was added to the oil and the solution concentrated in vacuo again. This was repeated to obtain a crystalline solid. The solid was dissolved in methanol and concentrated HCl  
10 and heated at reflux for 12 hours. The reaction was concentrated in vacuo and the residue was purified by silica gel flash chromatography (9:1 hexane/ $\text{Et}_2\text{O}$ ) to provide the pure aldehyde.

15 A solution of 1 equivalent of the aldehyde in THF was cooled to  $-78^\circ\text{C}$  and 1.1 equivalents of 0.5M ethynylmagnesium bromide/THF was added. After stirring the reaction at room temperature for 3 hours, it was diluted with  $\text{Et}_2\text{O}$  and washed twice with 10% citric acid.  
20 The combined aqueous layers were back-extracted once with  $\text{Et}_2\text{O}$ . The combined organic layers were washed twice with saturated aqueous  $\text{NaHCO}_3$ , dried over  $\text{MgSO}_4$  and concentrated in vacuo. The residue was purified by silica gel flash chromatography (4:1 to 3:2 hexane/ $\text{Et}_2\text{O}$ ) to  
25 provide the pure alkyne.

1 equivalent of 1-chloro-3-iodobenzene was dissolved in  $\text{EtOAc}$  and the solution was degassed by passing  $\text{N}_2$  through a pipette and into the solution for 10 minutes. 1.25  
30 equivalents of the alkyne was added, followed by 0.02 equivalents of dichlorobis(triphenylphosphine)palladium-(II), 0.04 equivalents of  $\text{CuI}$  and 5 equivalents TEA. The reaction was stirred for 14 hours, diluted with  $\text{EtOAc}$ , washed twice with 5%  $\text{Na}_2\cdot\text{EDTA}$ , brine and then dried over  
35  $\text{MgSO}_4$  and concentrated in vacuo. The residue was purified by silica gel flash chromatography (gradient elution, using  $\text{Et}_2\text{O}$  to  $\text{EtOAc}$ ) to provide the pure aryl alkyne.

5 1 equivalent of the aryl alkyne was dissolved in MeOH and the solution was degassed by passing N<sub>2</sub> through a pipette and into the solution for 10 minutes. The 5% Rh/Al<sub>2</sub>O<sub>3</sub> was added, one balloon-full of hydrogen was passed through the solution, and the reaction was stirred under an  
10 atmosphere of H<sub>2</sub> (using a balloon) for 7 hours, after which the reaction was filtered through a pad of celite and concentrated *in vacuo*. The residue was purified by silica gel flash chromatography (gradient elution, using Et<sub>2</sub>O to EtOAc) to provide the pure product.

15 2.3 equivalents of lithium iodide was added to 1 equivalent of the methyl ester in pyridine, and the mixture heated at reflux for 8 hours. The reaction was concentrated *in vacuo* and the residue was partitioned  
20 between EtOAc and 1N HCl. The aqueous layer was extracted three times with EtOAc, and the combined organic layers were washed with 1M NaHCO<sub>3</sub>, dried over MgSO<sub>4</sub> and concentrated *in vacuo*. The residue was dissolved in NMM and the solution concentrated *in vacuo*. The residue was  
25 taken up in DCM and then washed three times with 1N HCl. The organic layer was dried over MgSO<sub>4</sub> and concentrated *in vacuo* to provide the benzoic acid in high enough purity to be used without further purification.

30 1 equivalent of the acid, 2 equivalents of commercially available β- Boc- diaminopropionic acid methyl ester, 2 equivalents of EDC, 1 equivalent of Hobt and 3 equivalents of DIPEA were dissolved DMA. The reaction was stirred at room temperature and monitored by TLC (9/1  
35 DCM/MeOH). Upon completion, the mixture was concentrated *in vacuo*. The resulting oil was re suspended in Et<sub>2</sub>O and washed twice with 0.1 N H<sub>2</sub>SO<sub>4</sub>, twice with saturated NaHCO<sub>3</sub>, and once with brine. The organic layer was then

5       dried over  $\text{MgSO}_4$ , filtered and concentrated *in vacuo*. The residue was then purified on silica gel using 5% methanol in DCM as eluent to provide pure methyl ester.

10       1 equivalent of commercially available D-hydroxy proline was dissolved in a 3:2 THF/ $\text{H}_2\text{O}$  solution. 1.1 equivalents of solid  $\text{NaHCO}_3$  and 1.1 equivalents of  $\text{Boc}_2\text{O}$  were added and the mixture was stirred overnight. The reaction was concentrated to remove the THF, and the resulting aqueous  
15       layer was partitioned with hexanes. The aqueous layer was then acidified to pH 2 with 1N HCl and then partitioned twice with EtOAc. The combined organic layers were dried over  $\text{MgSO}_4$  and concentrated *in vacuo*. The resulting N-Boc-D-hydroxy proline was used without further purification.

20       The Boc protected amine was dissolved in a solution of TFA in DCM (1:1). After 20 minutes, the reaction was concentrated *in vacuo*. The resulting oil was dissolved in toluene and then reconcentrated *in vacuo*. 1 equivalent of  
25       this amine, 2 equivalents of Boc-D-hydroxy proline, 2 equivalents of EDC, 1 equivalent of HOBt and 3 equivalents of DIPEA were dissolved in DMA. The reaction was stirred at room temperature and monitored by TLC (9/1 DCM/MeOH). Upon completion, the mixture was concentrated  
30       *in vacuo*. The resulting oil was re suspended in  $\text{Et}_2\text{O}$  and washed twice with 0.1 N  $\text{H}_2\text{SO}_4$ , twice with saturated  $\text{NaHCO}_3$ , and once with brine. The organic layer was then dried over  $\text{MgSO}_4$ , filtered and concentrated *in vacuo*. The residue was then purified on silica gel using 5% methanol  
35       in DCM as eluent to provide pure methyl ester.

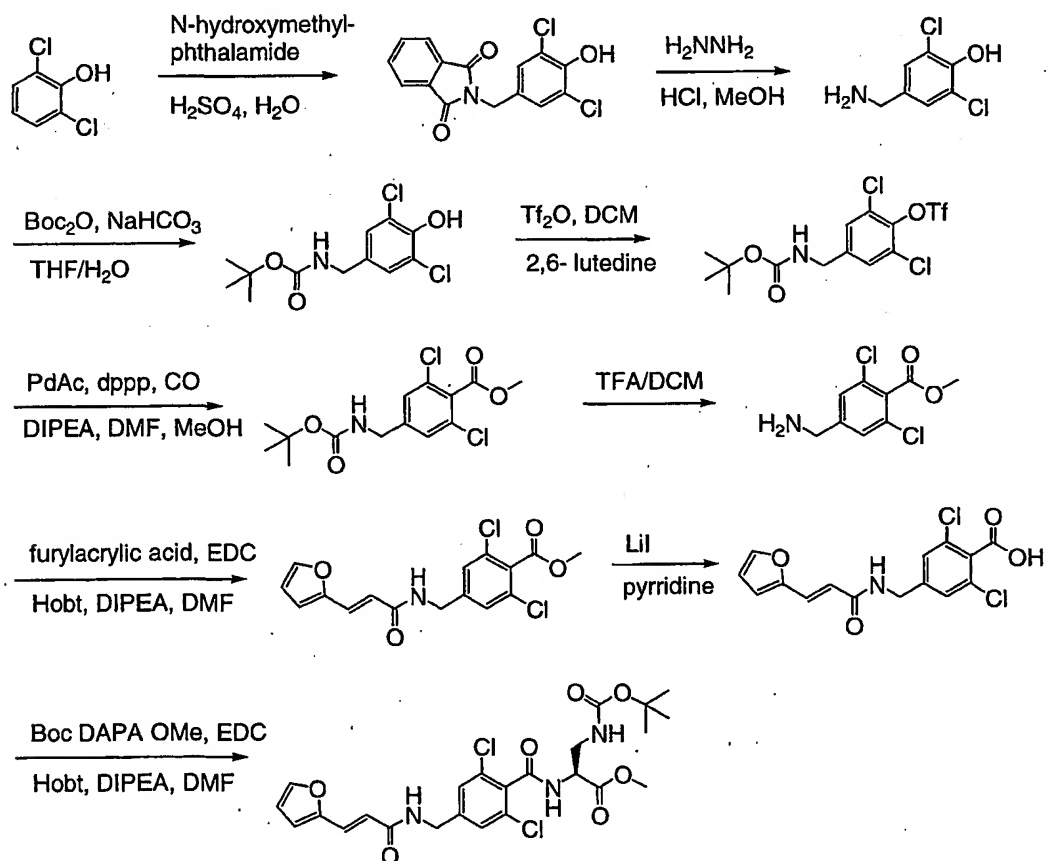
1 equivalent of the resultant methyl ester was dissolved in THF/ $\text{H}_2\text{O}$  (3/1) and 3 equivalents of  $\text{LiOH}\cdot\text{H}_2\text{O}$  was added.



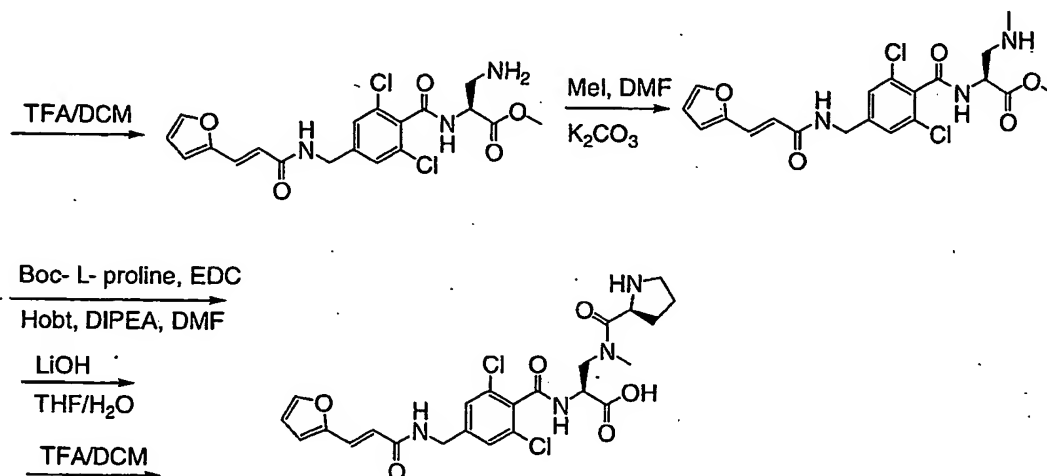
5 The reaction was monitored by TLC (9/1 DCM/MeOH). Upon completion, the mixture was acidified to pH 2 with 1M HCl and then concentrated *in vacuo*. The resulting solid was re suspended in Et<sub>2</sub>O and washed twice with 0.1 M HCl and once with brine. The organic layer was then dried over  
 10 MgSO<sub>4</sub>, filtered and concentrated *in vacuo*. The Boc, silyl residue was dissolved in a solution of TFA in DCM (1:1). After 20 minutes, the reaction was concentrated *in vacuo*. The resulting oil was dissolved in toluene and then reconcentrated *in vacuo*. The resulting acid was then  
 15 purified by reverse phase HPLC, verified by electrospray mass spectrometry and lyophilized to a powder.

# EXAMPLE 10      Synthesis of compound 35

20



25



10 A round bottom flask<sup>a</sup> was equipped with an efficient overhead stirrer and charged with concentrated H<sub>2</sub>SO<sub>4</sub> (2.7 x volume of H<sub>2</sub>O) and H<sub>2</sub>O and cooled to --5°C with an ethanol/ice bath. Once cool, 1 equivalent 2,6 dichloro phenol and 1 equivalent of N-(hydroxymethyl)phthalimide were added with vigorous stirring. The reaction was kept

15 cool for 4 hours and then allowed to warm to room temperature overnight with constant stirring. The reaction generally proceeds to a point where there was just a solid in the round bottom flask. At this point EtOAc and H<sub>2</sub>O were added and stirred into the solid. Large

20 chunks were broken up and then the precipitate was filtered and washed with more EtOAc and H<sub>2</sub>O. The product was then used without further purification after drying overnight under vacuum.

25 1 equivalent of the dry product and methanol (22.5ml x #g of starting material) was added to a round bottom flask equipped with a H<sub>2</sub>O condenser and stirring bar. 1.2 equivalents of hydrazine mono hydrate was added and the mixture refluxed for 4 hours. After cooling to room

30 temperature, concentrated HCl (4.5ml x #g of starting material) was carefully added. Upon completion of the

5 addition, the mixture was refluxed overnight (> 8 hours). The reaction was cooled to 0°C and the precipitated by-product was removed by filtration. The filtrate was then concentrated in vacuo.

10 The crude amine residue was dissolved in a 3:2 THF/H<sub>2</sub>O solution. 1.1 equivalents of solid NaHCO<sub>3</sub> and 1.1 equivalents of Boc<sub>2</sub>O were added and the mixture was stirred overnight. The reaction was concentrated, and the residue was partitioned between H<sub>2</sub>O and Et<sub>2</sub>O. The aqueous  
15 layer was extracted with Et<sub>2</sub>O and the combined organic layers were dried over MgSO<sub>4</sub> and concentrated in vacuo to a solid. Recrystallization from hot methanol and H<sub>2</sub>O provided pure product.

20 1 equivalent of the Boc protected amine and 1.5 equivalents of 2, 6- lutidine was dissolved, with mild heating if necessary, in DCM in a round bottom flask. Once the starting material has completely dissolved, the mixture was cooled to -78°C under N<sub>2</sub> with a dry ice  
25 ethanol bath. Once cool, 2.5 equivalents of triflic anhydride was added and the reaction was allowed to slowly come to room temperature with stirring. The reaction was monitored by TLC and was generally done in 4 hours. Upon completion, the reaction was concentrated in  
30 vacuo and the residue partitioned between EtOAc and H<sub>2</sub>O. The organic layer was washed twice with 0.1N H<sub>2</sub>SO<sub>4</sub>, twice with saturated NaHCO<sub>3</sub>, once with brine, dried over MgSO<sub>4</sub> and concentrated in vacuo. The residue was then purified on silica gel using DCM as eluent to provide pure  
35 triflate.

1 equivalent of triflate was dissolved in DMF and MeOH in the glass insert of a high pressure Parr bomb. The

5 starting material was then degassed while stirring with  
CO for 10 minutes. 0.15 equivalents palladium(II) acetate  
and 0.15 equivalents of 1, 3- bis(diphenylphosphino)  
propane were then added and the mixture was then degassed  
while stirring with CO for another 10 minutes at which  
10 time 2.5 equivalents of diisopropyl ethyl amine was  
added. After properly assembling the bomb, it was charged  
with 300psi CO gas and heated to 70°C with stirring  
overnight. The bomb was then cooled and vented. The  
mixture was transferred to a round bottom flask and  
15 concentrated *in vacuo*. The residue was then purified on  
silica gel using DCM with 1% acetone and 1% TEA as eluent  
to provide pure methyl ester.

The Boc protected amine was dissolved in a solution of  
20 TFA in DCM (1:1). After 20 minutes, the reaction was  
concentrated *in vacuo*. The resulting oil was dissolved in  
toluene and then reconcentrated *in vacuo*. The TFA salt of  
the amine was dissolved in Et<sub>2</sub>O and washed twice with a  
10% solution of K<sub>2</sub>CO<sub>3</sub> in H<sub>2</sub>O and once with brine. The  
25 organic layer was then dried over MgSO<sub>4</sub>, filtered and  
concentrated *in vacuo*.

1 equivalent of the free based amine, 3 equivalents of  
furylacrylic acid, 3 equivalents of EDC and 1 equivalent  
30 of Hobt were dissolved DMA. The reaction was stirred at  
room temperature and monitored by TLC (9/1 DCM/MeOH).  
Upon completion, the mixture was concentrated *in vacuo*.  
The resulting oil was re suspended in Et<sub>2</sub>O and washed  
twice with 0.1 N H<sub>2</sub>SO<sub>4</sub>, twice with saturated NaHCO<sub>3</sub>, and  
35 once with brine. The organic layer was then dried over  
MgSO<sub>4</sub>, filtered and concentrated *in vacuo*. The residue was  
then purified on silica get using 5% methanol in DCM as  
eluent to provide pure methyl ester.

5

2.3 equivalents of lithium iodide was added to 1 equivalent of the methyl ester in pyridine, and the mixture heated at reflux for 8 hours. The reaction was concentrated *in vacuo* and the residue was partitioned between EtOAc and 1N HCl. The aqueous layer was extracted three times with EtOAc, and the combined organic layers were washed with 1M NaHCO<sub>3</sub>, dried over MgSO<sub>4</sub> and concentrated *in vacuo*. The residue was dissolved in NMM and the solution concentrated *in vacuo*. The residue was taken up in DCM and then washed three times with 1N HCl. The organic layer was dried over MgSO<sub>4</sub> and concentrated *in vacuo* to provide the benzoic acid in high enough purity to be used without further purification.

1 equivalent of the acid, 2 equivalents of commercially available  $\beta$ -Boc-diaminopropionic acid methyl ester, 2 equivalents of EDC, 1 equivalent of Hobt and 3 equivalents of DIPEA were dissolved DMA. The reaction was stirred at room temperature and monitored by TLC (9/1 DCM/MeOH). Upon completion, the mixture was concentrated *in vacuo*. The resulting oil was re suspended in Et<sub>2</sub>O and washed twice with 0.1 N H<sub>2</sub>SO<sub>4</sub>, twice with saturated NaHCO<sub>3</sub>, and once with brine. The organic layer was then dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo*. The residue was then purified on silica gel using 5% methanol in DCM as eluent to provide pure methyl ester.

The Boc protected amine was dissolved in a solution of TFA in DCM (1:1). After 20 minutes, the reaction was concentrated *in vacuo*. The resulting oil was dissolved in toluene and then re concentrated *in vacuo*.

5 To 1 equivalent of this amine was added 1.05 equivalents  
of methyl iodide and 2.1 equivalents potassium carbonate  
in DMF. The reaction was stirred at room temperature and  
followed by TLC (9/1 DCM/MeOH). Upon completion of the  
10 reaction, it was diluted with EtOAc and H<sub>2</sub>O. The aqueous  
layer was partitioned again with EtOAc and the combined  
organic layers washed with brine, dried over MgSO<sub>4</sub> and  
concentrated *in vacuo*.

1 equivalent of this amine, 2 equivalents of Boc-L-  
15 thiazolidine-4-carboxylic acid, 2 equivalents of EDC, 1  
equivalent of H<sub>2</sub>O and 3 equivalents of DIPEA were  
dissolved in DMA. The reaction was stirred at room  
temperature and monitored by TLC (9/1 DCM/MeOH). Upon  
completion, the mixture was concentrated *in vacuo*. The  
20 resulting oil was re suspended in Et<sub>2</sub>O and washed twice  
with 0.1 N H<sub>2</sub>SO<sub>4</sub>, twice with saturated NaHCO<sub>3</sub>, and once  
with brine. The organic layer was then dried over MgSO<sub>4</sub>,  
filtered and concentrated *in vacuo*. The residue was then  
purified on silica gel using 5% methanol in DCM as eluent  
25 to provide pure methyl ester.

1 equivalent of the resultant methyl ester was dissolved  
in THF/H<sub>2</sub>O (3/1) and 3 equivalents of LiOH·H<sub>2</sub>O was added.  
The reaction was monitored by TLC (9/1 DCM/MeOH). Upon  
30 completion, the mixture was acidified to pH 2 with 1M HCl  
and then concentrated *in vacuo*. The resulting solid was  
re suspended in Et<sub>2</sub>O and washed twice with 0.1 M HCl and  
once with brine. The organic layer was then dried over  
MgSO<sub>4</sub>, filtered and concentrated *in vacuo*.

35 The residue was dissolved in a solution of TFA in DCM  
(1:1). After 20 minutes, the reaction was concentrated *in*  
*vacuo*. The resulting oil was dissolved in toluene and  
then re concentrated *in vacuo*. The resulting acid was

5 then purified by reverse phase HPLC, verified by electrospray mass spectrometry and lyophilized to a powder.

10

#### EXAMPLE 11 PLM2 Antibody Capture LFA-1:ICAM-1 Assay

A non-function blocking monoclonal antibody against human CD18, PLM-2 (as described by Hildreth, et al., *Molecular Immunology*, Vol. 26, No. 9, pp. 883-895, 1989), is  
15 diluted to 5µg/ml in PBS and 96-well flat-bottomed plates are coated with 100µl/well overnight at 4°C. The plates are blocked with 0.5% BSA in assay buffer (0.02M Hepes, 0.15M NaCl, and 1mM MnCl<sub>2</sub>) 1h at room temperature.  
20 Plates are washed with 50mM Tris pH 7.5, 0.1M NaCl, 0.05% Tween 20 and 1mM MnCl<sub>2</sub>. Purified full-length recombinant human LFA-1 protein is diluted to 2µg/ml in assay buffer and 100µl/well is added to plates and incubated 1h at 37°C. Plates are washed 3X. 50µl/well  
25 inhibitors, appropriately diluted in assay buffer, are added to a 2X final concentration and incubated for 30' at 37°C. 50µl/well of purified recombinant human 5 domain ICAM-Ig, diluted to 161ng/ml (for a final concentration of 80ng/ml) in assay buffer, is added and  
30 incubated 2h at 37°C. Plates are washed and bound ICAM-Ig is detected with Goat anti-HuIgG(Fc)-HRP for 1h at room temperature. Plates are washed and developed with 100µl/well TMB substrate for 5-10' at room temperature. Colorimetric development is stopped with 100µl/well 1M  
35 H<sub>3</sub>PO<sub>4</sub> and read at 450nm on a platereader. Results of the PLM2 assay are shown in tables 1-4 below.

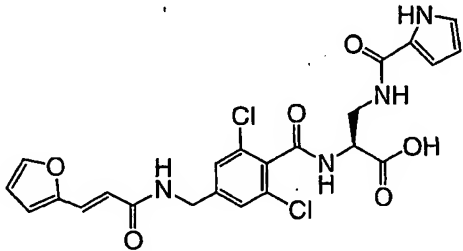
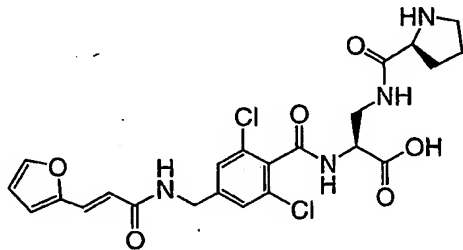
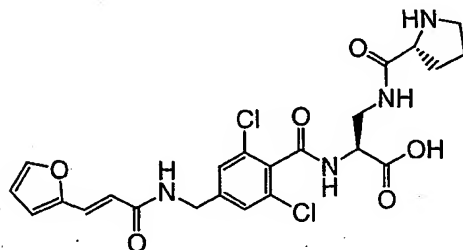
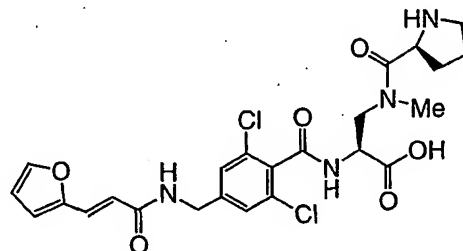
## 5      EXAMPLE 12            serum/plasma protein binding

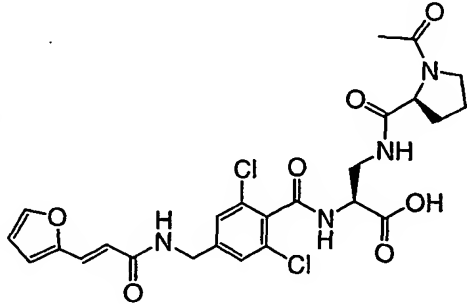
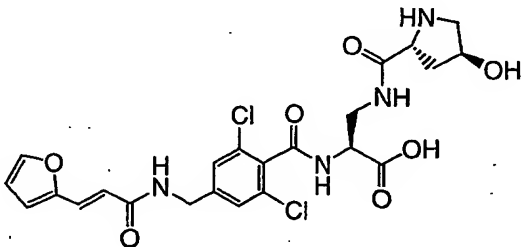
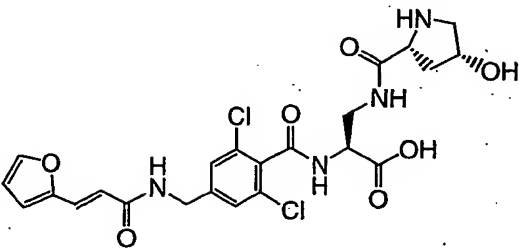
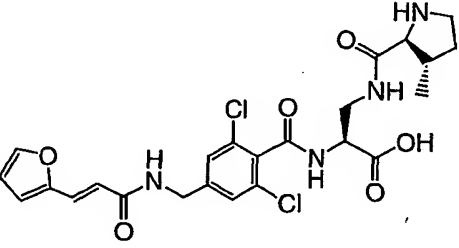
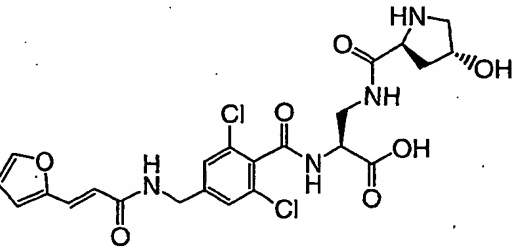
Binding of test compounds was performed according to procedures described in Borga et al (Journal of Pharmacokinetics & Biopharmaceutics, 1997, 25(1):63-77) and Godolphin et al (Therapeutic drug monitoring, 1983, 5:319-23). Duplicate samples of 10  $\mu$ l of test compound stock solution (1  $\mu$ g/ $\mu$ L) was spiked into 1 mL of either buffer or serum/plasma adjusted to pH 7.4 using CO<sub>2</sub> at room temperature. Samples were equilibrated by incubating vials in a water bath with shaker at 37°C for 15 minutes. 200  $\mu$ l of the buffer spiked sample was saved as prefiltrate. 800  $\mu$ l of buffer spiked samples and 1 ml of serum spiked samples were centrifuged at 1500 g, 37°C, for 30 minutes in a Centrifree ultrafiltration device (Amicon Inc.). Pre and post-filtrates were then analyzed by LC/MS-MS and percent binding of test compound to serum/plasma protein was determined from the post and prefiltrates accounting for any non-specific binding determined from the buffer control.

25      Compounds of the invention incorporating a non-aromatic ring at substituent Cy surprisingly exhibit low serum plasma protein binding characteristics which is advantageous for maintaining therapeutically relevant serum levels. As illustrated in tables 1-4, reference compounds (ref) having an aromatic ring at substituent Cy consistently show higher % plasma protein binding compared to the equivalent compound of the invention having a non-aromatic ring.



5 table 1

cmpd no.	LFA-1 PLM2 IC <sub>50</sub> ( $\mu$ M)	Mac-1 IC <sub>50</sub> ( $\mu$ M)	% plasma protein binding	structure
ref	0.071		98.3	
4	0.004		82.9	
5	0.008		83.1	
35	0.009		51.36	

17	0.003		84.61	
10	0.003		65.91	
12	0.002		79.48	
13	0.004		77.58	
14	0.002		72.60	

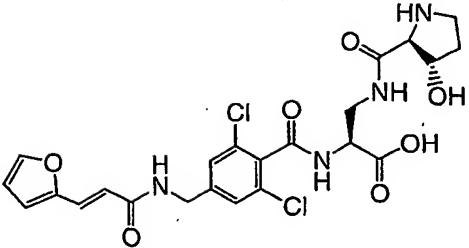
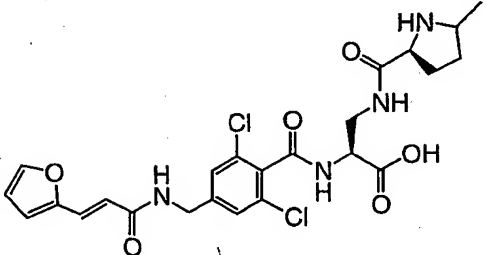
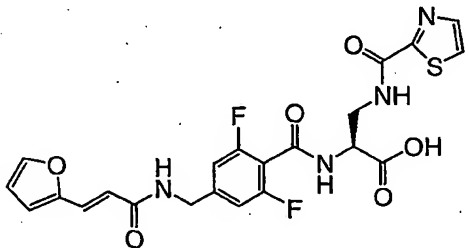
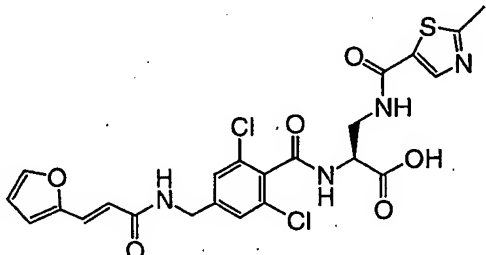
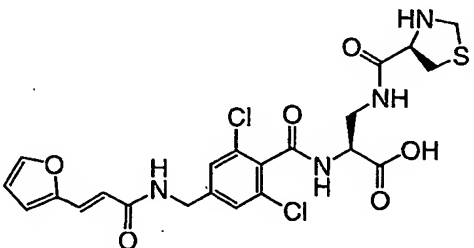
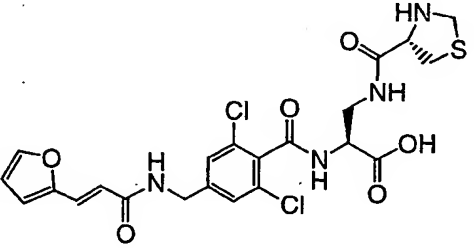
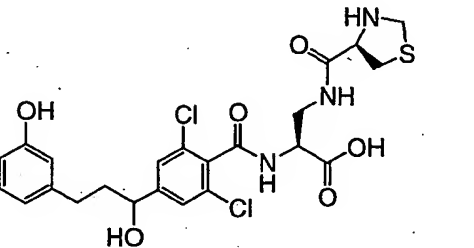
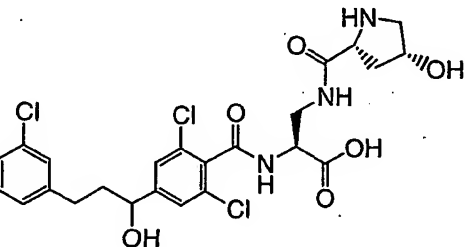
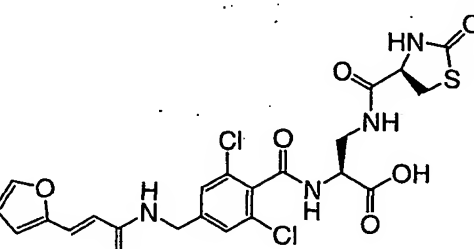
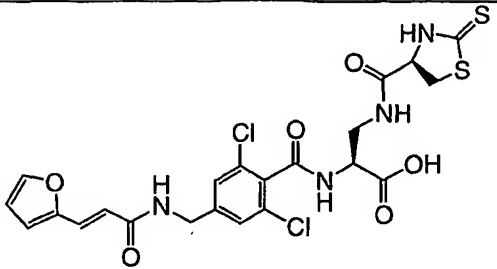
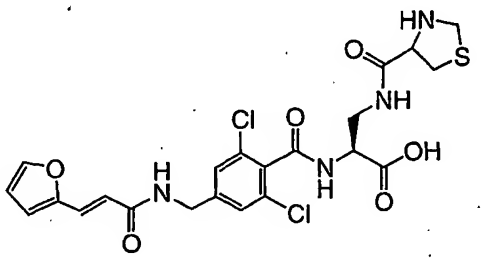
41	0.003		84.83	
44	0.002		82.97	

table 2

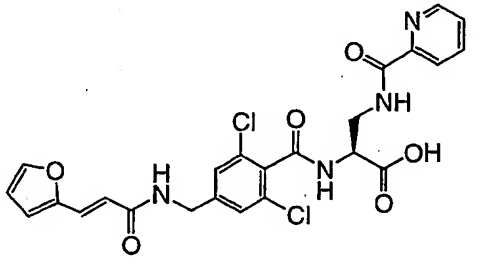
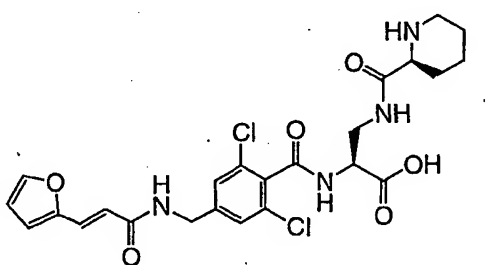
cmpd no.	LFA-1 PLM2 IC <sub>50</sub> ( $\mu$ M)	Mac-1 IC <sub>50</sub> ( $\mu$ M)	% plasma protein binding	structure
ref	0.005		98.12	
ref	0.004	161	99.5	

6	0.007	2509	95.43	
15	0.004		92.51	
36	0.002	65	92.84	
37		35.54	93.19	
38	0.012	7609	93.29	

40	0.002	1427	96.93	
42	0.003		91.4	

5

table 3

compd no.	LFA-1 PLM2 IC <sub>50</sub> ( $\mu$ M)	Mac-1 IC <sub>50</sub> ( $\mu$ M)	% plasma protein binding	structure
ref	0.015		99.4	
9	0.002		77.17	

5

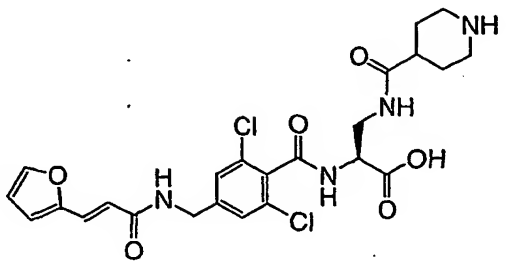
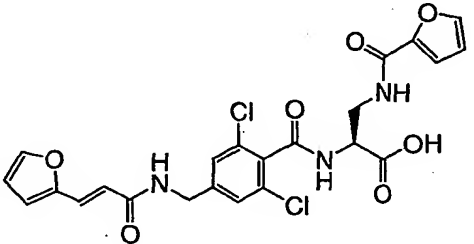
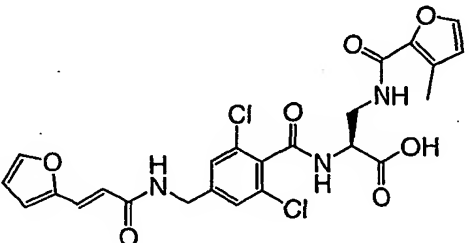
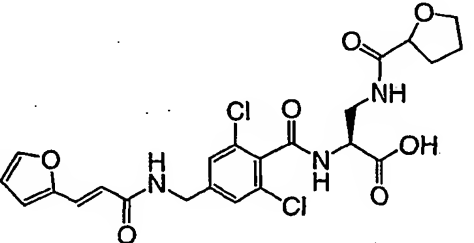
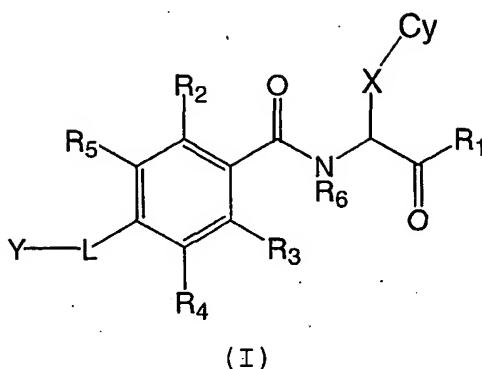
3	0.011		80.8	
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table 4

compd no.	LFA-1 PLM2 IC <sub>50</sub> ( $\mu$ M)	Mac-1 IC <sub>50</sub> ( $\mu$ M)	% plasma protein binding	structure
ref			99.2	
ref	0.002	1683	99.70	
51	0.005	2362	92.8	

5 WE CLAIM:

1. A compound of formula (I)



wherein

- 10 Cy is a non-aromatic carbocycle or heterocycle optionally substituted with hydroxyl, mercapto, thioalkyl, halogen, oxo, thio, amino, aminoalkyl, amidine, guanidine, nitro, alkyl, alkoxy or acyl;
- 15 X is a divalent hydrocarbon chain optionally substituted with hydroxyl, mercapto, halogen, amino, aminoalkyl, nitro, oxo or thio and optionally interrupted with N, O, S, SO or SO<sub>2</sub>;
- 20 Y is a carbocycle or heterocycle optionally substituted with hydroxyl, mercapto, halogen, oxo, thio, thioalkyl, amino, aminoalkyl, carbocycle or heterocycle ring, hydrocarbon, a halo-substituted hydrocarbon, amino, amidine, guanidine, cyano, nitro, alkoxy or acyl;
- 25 L is a bond or a divalent hydrocarbon chain optionally substituted hydroxyl, halogen, oxo or thio and optionally interrupted with N, O, S, SO or SO<sub>2</sub> or an amino acid residue; less than 3 or 5 atoms
- 30 R<sub>1</sub> is H, OH, amino, O-carbocycle or alkoxy optionally substituted with amino, a carbocycle or heterocycle;

5           R<sub>2-5</sub> are independently H, hydroxyl, mercapto, halogen, cyano, amino, amidine, guanidine, nitro or alkoxy; or R<sub>3</sub> and R<sub>4</sub> together form a fused carbocycle or heterocycle optionally substituted with hydroxyl, halogen, oxo, thio, amino, amidine, 10           guanidine or alkoxy; .

          R<sub>6</sub> is H or a hydrocarbon chain optionally substituted with a carbocycle or a heterocycle; and salts, solvates and hydrates thereof; with the proviso that when Y is phenyl, R<sub>2</sub>, R<sub>4</sub> and R<sub>5</sub> 15           are H, R<sub>3</sub> is Cl and R<sub>1</sub> is OH then X is other than cyclohexyl.

2.   A compound according to claim 1, wherein Cy is a 5- or 6-member non-aromatic heterocycle optionally 20           substituted with hydroxyl, mercapto, thioalkyl halogen, oxo, thio, amino, aminoalkyl, amidine, guanidine, nitro, alkyl, alkoxy or acyl.
3.   A compound according to claim 2, wherein said 25           heterocycle comprises one or two heteroatoms and is optionally substituted with hydroxyl, oxo, mercapto, thio, alkyl or alkanoyl.
4.   A compound according to claim 3, wherein said 30           heterocycle is selected from the group consisting of piperidine, piperazine, morpholine, tetrahydrofuran, tetrahydrothiophene, oxazolidine, cyclopropa-pyrrolidine and thiazolidine optionally substituted with hydroxy, oxo, mercapto, thio, alkyl or 35           alkanoyl.
5.   A compound according to claim 4, wherein said heterocycle is selected from the group consisting of



- 5           piperidine, piperazine, morpholine, tetrahydrofuran,  
tetrahydrothiophene, oxazolidine, thiazolidine  
optionally substituted with hydroxy, oxo, mercapto,  
thio, alkyl or alkanoyl.
- 10       6.   A compound according to claim 1, wherein Cy is a 3-6  
member carbocycle optionally substituted with  
hydroxyl, mercapto, halogen, oxo, thio, amino,  
amidine, guanidine, alkyl, alkoxy or acyl.
- 15       7.   A compound according to claim 6, wherein said  
carbocycle is partially unsaturated.
- 20       8.   A compound according to claim 7, wherein Cy is  
cyclopropyl, cyclopropenyl, cyclobutyl, cyclobutenyl,  
cyclopentyl, cyclopentenyl cyclohexyl or  
cyclohexenyl.
- 25       9.   A compound according to claim 1, wherein X is a C<sub>1-5</sub>  
divalent hydrocarbon optionally having one or more  
carbon atoms replaced with N, O, S, SO or SO<sub>2</sub> and  
optionally being substituted with hydroxyl, oxo or  
thio.
- 30       10.  A compound according to claim 1, wherein X is -CH<sub>2</sub>-  
NR<sub>6</sub>-C(O)- wherein the carbonyl -C(O)- portion thereof  
is covalently bound to Cy and R<sub>6</sub> is H or alkyl.
- 35       11.  A compound according to claim 1, wherein Y is a  
carbocycle or heterocycle optionally substituted  
with hydroxyl or halogen.
12.   A compound according to claim 11, wherein Y is  
furan-2-yl, thiophene-2-yl or phenyl, wherein said

- 5           phenyl is optionally substituted with halogen or hydroxyl.
13. A compound according to claim 1, wherein L is a divalent hydrocarbon optionally having one or more  
10 carbon atoms replaced with N, O, S, SO or SO<sub>2</sub> and optionally being substituted with hydroxyl, halogen oxo or thio; or three carbon atoms of the hydrocarbon are replaced with an amino acid residue.
14. A compound according to claim 13, wherein L is -  
15 CH=CH-C(O)-NR<sub>6</sub>-CH<sub>2</sub>-, -CH<sub>2</sub>-NR<sub>6</sub>-C(O)-, -C(O)-NR<sub>6</sub>-CH<sub>2</sub>-, -CH(OH)-(CH<sub>2</sub>)<sub>2</sub>-, -(CH<sub>2</sub>)<sub>2</sub>-CH(OH)-, -(CH<sub>2</sub>)<sub>3</sub>-, -C(O)-NR<sub>6</sub>-CH(R<sub>7</sub>)-C(O)-NR<sub>6</sub>-, -NR<sub>6</sub>-C(O)-CH(R<sub>7</sub>)-NR<sub>6</sub>-C(O)-, -CH(OH)-CH<sub>2</sub>-O- or -CH(OH)-CF<sub>2</sub>-CH<sub>2</sub>- wherein each R<sub>6</sub> is  
20 independently H or alkyl and R<sub>7</sub> is an amino acid side chain.
15. A compound according to claim 14, wherein R<sub>1</sub> is H, OH, amino, O-carbocycle or alkoxy optionally  
25 substituted with a carbocycle.
16. A compound according to claim 15, wherein R<sub>1</sub> is H or C<sub>1-4</sub> alkyloxy.
17. A compound according to claim 1, wherein at least  
30 one of R<sub>2</sub> and R<sub>3</sub> is halogen and the other is H or halogen.
18. A compound according to claim 17, wherein R<sub>2</sub> and R<sub>3</sub>  
35 are both Cl.
19. A compound according to claim 18, wherein R<sub>4</sub> and R<sub>5</sub> are both H.

5

20. A pharmaceutical composition comprising a compound according to claim 1 with a pharmaceutically acceptable adjuvant, diluent or carrier.

10

21. A method of inhibiting binding of a LFA-1 to a protein ligand comprising contacting LFA-1 with a compound of claim 1.

22. A method of treating a disease or condition mediated by LFA-1 in a mammal comprising administering to said mammal an effective amount of a compound according to claim 1.

23. A method according to claim 23, wherein said disease or condition is arthritis, psoriasis, organ transplant rejection, asthma, and inflammatory bowel disease

15

23. A method of inhibiting an inflammatory disease or condition in a mammal comprising administering to said mammal an effective amount of a compound according to claim 1.

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D405/12 C07D417/12 C07D207/16 A61P37/06 A61K31/34  
 A61K31/425 A61K31/40 //(C07D405/12,307:00,207:00),  
 (C07D417/12,307:00,277:00)

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data, EPO-Internal

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 04247 A (ZHENG ZHONGLI ;ADAMS STEVEN P (US); BIOGEN INC (US); ENSINGER CARO) 5 February 1998 (1998-02-05) Tables 1 to 3; pages 162 to 183 claims 5,10,7	1-20
A	WO 00 39081 A (ABBOTT LAB) 6 July 2000 (2000-07-06) claims 12,13,20-23	1-20

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

## \* Special categories of cited documents:

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*Z\* document member of the same patent family

Date of the actual completion of the international search

6 June 2002

Date of mailing of the international search report

13/06/2002

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
 NL - 2280 HV Rijswijk  
 Tel (+31-70) 340-2040, Tx. 31 651 epo nl,  
 Fax (+31-70) 340-3016

Authorized officer

Goss, I

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1,2,3,6,7,9-20 Completely:4,5,8

Present claims 1 to 3 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds wherein Cy is nearer defined (namely according to claims 4, 5 and 8 or description page 21, lines 5 to 27).

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

## INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 01/44203

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